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URIC ACID

AS A

FACTOR IN THE CAUSATION OF DISEASE.

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URIC ACID

AS

A FACTOR IN THE CAUSATION OF DISEASE

A CONTRIBUTION TO THE

PATHOLOGY OF HIGH BLOOD PRESSURE, HEADACHE, EPILEPSY, NERVOUSNESS, MENTAL DISEASE, ASTHMA, HAY FEVER, PAROXYSMAL HÆMOGLOBINURIA, ANÆMIA, BRIGHT'S DISEASE, DIABETES, GOUT, RHEUMATISM, BRONCHITIS,

AND OTHER DISORDERS.

BY

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Seventh Edition

WITH SEVENTY-FIVE ILLUSTRATIONS

LONDON

J. & A. CHURCHILL

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PREFACE TO THE SEVENTH EDITION.

This Edition has been revised throughout, and since the chief points are now so well known it has been possible to avoid a certain amount of repetition, and thus to make room for new and important matter without increasing the size of the volume.

Additions have been made both to the clinical and experimental portions, and much new evidence adduced from various sources, especially with regard to the presence of uric acid in the blood and its relation to capillary circulation, blood pressure and blood quality in health and disease. Some new cases of the more important diseases have been added and some fresh contributions to the pathology of diabetes and chorea, together with some new experiences in treatment, both by drugs and diet. Considerable attention has also been given to the recent investigations of others on the quantity of food (albumen) required, and the diet notes I make use of in treatment have been added as an appendix.

Nothing has occurred to invalidate the main facts as given in preceding editions. The uric-acid-free diet cures or prevents as many functional and organic troubles as ever; but, begun when development is complete, it can, of course, not do much for development which is defective. The theoretical explanation of the results produced remains, as it has always been, to a large extent suggestive. Excess of uric acid can be removed quickly by drugs or more slowly by diet, and when this has been done we see some of the effects it has itself produced, as well as any organic or structural changes it has helped to mask or intensify. There is still much to learn in both these directions.

In some cases removal of uric acid is all that is required for the attainment of almost perfect health and strength, in others

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several generations may not suffice to remove defects of structure and development resulting, among other things, from the use through many generations of a diet at variance with the anatomy and physiology of man. If man is a carnivore, indeed if he is not a frugivore, the study of comparative anatomy has been a useless waste of time.

Flesh food has as yet been possible only for a small portion of the race, and till quite recent times its use in large quantity was still only possible for the richer fraction of that portion. It brought with it its own diseases, formerly confined to the rich, now spreading far and wide through all classes, hand in hand with the cheapening of flesh and tea. This volume suggests that these diseases can be prevented or cured by leaving out the poisons and reverting to the foods most in accord with the anatomy and physiology of man, which were more common here a century ago, and are still common in other countries. There can be no doubt, however, that here, as elsewhere, prevention is better than cure.

It must take several generations to undo even the effects of the food changes in this country in the last thirty or forty years, and longer still before the full import of the food problem and the action of uric acid, its influence on the parent, the child, the youth, the adult, or the old, become common knowledge. Then only will it be possible to say whether I have now claimed too much.

In previous editions I have mentioned the names of many to whom I have been greatly indebted for valuable suggestions, help and encouragement, but these are now so numerous that it is practically impossible to do so here. My debt, however, remains to all those previously mentioned, and to many more whose names occur again and again in this volume.

7, Brook Street, W.
May, 1908.

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URIC ACID

AS A

FACTOR IN THE CAUSATION OF DISEASE.

CHAPTER I.

History.

It is more than twenty-four years since I began the research of which I give an account in the following pages.

I thought it then a simple matter to investigate the causation and treatment of the headache from which I suffered, but the horizon has expanded, and I realise that a large portion of the field of medicine may be modified by my results.

The matter has gradually become simpler till it is clear that "uric acid disease" is only uric acid toxæmia; the poison is swallowed, and poisoning with its signs and symptoms inevitably results.

It is also clear that uric acid is a poison for all, and everyone who swallows it has sooner or later reason to regret the fact.

Having been a life-long sufferer from migraine, in the autumn of 1882, in despair of obtaining complete relief from drugs, and not without some fear that I was suffering from organic disease, I gave up butcher's meat and replaced it by milk and fish, the latter in decreasing quantities till milk and cheese formed my only animal foods.

I had tried many alterations in diet, including an increased allowance of meat and various alterations in quantity and quality of sugar, tea, coffee, and tobacco, without noticeable result. But on the meatless diet a change was apparent; my headaches diminished in

frequency and severity, and from an average of one in a week they fell, as the diet was continued, to one in a month, one in three, six, eight, or twelve months, until eighteen months elapsed without an attack of notable severity.

I have never returned to butcher's meat, because by avoiding it I obtain what is practically immunity from a disorder which bid fair to cripple me and prevent all mental and sedentary work.

If I presume on my security, if I dine in the usual way, and especially if I take meat and wine, I develop a more or less severe headache within two or three days, though I can now control the pain to a greater extent than formerly, as more correct knowledge of causation gives more complete means of resistance.

Having observed that discontinuance of butcher's meat relieved me of headache, I at first (*Practitioner*, 1884) was disposed to consider the formation of some poison, possibly of the nature of a ptomaine, in the intestines during digestion.

A further study of the clinical history of migraine brought out, however, so strong a relationship to gout that (*Practitioner*, 1886) I began to suspect uric acid might be the poison I was seeking. I therefore proceeded to estimate the excretion of uric acid and urea.

At first I estimated only the excretion of twenty-four hours, and as many of my headaches lasted only a portion of a day, I got indefinite or contradictory results; but when I separated the urine excreted during the headache from that before and after it, a definite relation between headache and excretion of uric acid became apparent—a relation I have since found in myself and others, in instances quite sufficient to remove the result from the chapter of accidental coincidences. The headache in question, has important concomitant symptoms, slow high tension pulse, cold surface and extremities, mental depression, and disinclination for exertion, mental or bodily, and the urine during the headache is scanty and of high colour and specific gravity.

Having noticed the relation of this headache to the excretion of uric acid I observed that each of its symptoms bore exactly the same relation; that when the pulse was slow and of high tension there was always a greater excretion of uric acid than when it presented the opposite character, and the same with the mental depression and scanty urine.

Further experiment disclosed the fact that the excretion of uric acid was within my control, and that I could alter it daily or hourly (*Journal of Physiology*, vol. viii.).

I observed that in altering uric acid I could alter the related symptoms; that when I produced increased excretion with alkali, headache, mental depression, cold surface, slow pulse and scanty urine followed, and that when I stopped the plus excretion with an acid these symptoms ceased; so that not only had I power to produce or remove the headache but also to free or obstruct the capillaries, to affect the tension of the pulse, and the rate of the heart's action, and thus to influence the circulation in brain, skin, kidneys, and probably the whole body.

I noticed that in curing a headache by giving an acid to diminish excretion of uric acid, I always produced a certain amount of pricking and shooting pain in my joints (generally in those most used on the day in question), and it occurred to me that the uric acid was retained in these joints and produced the pains. Failing to appear in the urine it must have gone somewhere. What more natural than to suppose that it had been retained in the joints (where in gout it is found), and that the pricking pains denoted its presence?

On turning to Sir A. Garrod I found he had described similar joint pains as occurring in gouty subjects after the ingestion of beer or wine, and a little investigation proved that all beers and wines are strongly acid, so that a simple explanation existed.

I have since ascertained that this was a single instance of a general law, and that all substances increasing the solubility of uric acid increase its excretion in the urine and do good in the joint troubles due to its irritating presence; while conversely all substances diminishing the solubility of uric acid, diminish its excretion in the urine and increase these irritations in joints and other fibrous structures. And the capillary circulation reveals where the uric acid will be found, whether in the blood (in which case the circulation will be slow), or in the fibrous tissues outside the vessels in which case the circulation will be quick in proportion as the blood contains little uric acid. Briefly, uric acid can now be seen as it passes through the circulation.

On such comparatively simple facts and observations my writings are based, and I have been led to reason on the pathology of epilepsy (in some cases of which I found exactly similar fluctuations in the excretion of uric acid to those met with in migraine, thus explaining a long-known clinical relationship between the two diseases)—of rheumatism and rheumatoid disease, the causation of Bright's disease, and diabetes, Raynaud's disease, and paroxysmal hæmoglobinuria and anæmia.

But if uric acid affects the capillaries thus and to the extent I claim, it must influence for good or evil the function, nutrition and structure of every organ and tissue, from the skin to the most central fibres of the spinal cord and brain. And, observing the effects produced by uric acid in causation of fatigue and its influence on the rise and fall in formation and excretion of urea, I think few can fail to admit its power over the metabolism of the whole body (see "Diet and Food," chapters i. and ii.). It is demonstrable also that the capillary circulation of a meat and tea consumer is much slower than that of the abstainer.

Naturally the subject is not so simple as might appear from this outline, but that will be evident in later detail, and I shall as far as possible conduct my reader through my own course of reasoning.

I will first cite some passages in the writings of Sir A. Garrod, Dr. Liveing and others, which have influenced me in the course of my investigations.

Sir Alfred Garrod says ("Gout and Rheumatic Gout," ed. iii., p. 6): "Galen, who lived about the latter half of the second century, was of opinion that gout was caused by some unnatural accumulation of matters in the part affected. These matters were supposed to consist of phlegm, bile, blood, or a mixture of these fluids, and chalk-stones were considered to be formed by their concretion or solidification."

Our own knowledge might be expressed in almost the same words if "uric acid" be substituted for "phlegm, bile and blood."

Sir A. Garrod also says (p. 2, prev. ref.): "It is by no means rare to hear of inflammation of a joint by one practitioner called gout, by another rheumatism, and by a third rheumatic gout." If it appears that my work tends to show that these more or less distinct clinical conditions may all be due to accumulation of uric acid, I hope this will be regarded as an advance, in that, with greater knowledge of its chemical and physical properties, we are now able to understand how it may produce very different clinical pictures according to its time of action, its quantity, and the metabolic activity as well as the structure, vascularity and general anatomical arrangement of the tissue on which it acts.

We may consider, therefore, that these discrepancies of opinion reflect credit on our profession, as failing to detect essential differences where nature had placed none. Further on Sir A.

Garrod says (p. 275), "The causes which predispose to gout independently of individual peculiarity are either such as produce an increased formation of uric acid in the system, or lead to its retention in the blood."

And in the Lumleian Lectures (*British Medical Journal*, January, 1883, p. 549), he says, "May it not be the case that when uric acid exists in the blood it is attracted differently by different organs, and thus the spleen and liver more frequently contain appreciable quantities than other tissues? Or, again, may it not be that in some organs, as the spleen, the substance of which, if not acid during life rapidly becomes so after death, while the blood remains strongly alkaline, the uric acid becomes less soluble and more easily retained."

I was led, without knowledge of Sir A. Garrod's remarks, to believe that excess of uric acid in the blood and body is almost never due to increased formation, but generally to retention or failure of excretion; and being always able with alkalies to increase and with acids to diminish the excretion, I adopted (*Journal of Physiology*, vol. viii.) Sir A. Garrod's above-quoted suggestion to explain my results, and have continued to use it.

With regard to lead Sir A. Garrod says (p. 243), "It would appear, therefore, that in individuals impregnated with lead the blood becomes loaded with uric acid, not from its increased formation, but from its imperfect excretion."

My researches apparently show that the blood never becomes loaded with uric acid save from excessive introduction (flesh, tea, &c.), followed by, or acting in conjunction with imperfect excretion, and this imperfect excretion (or retention) will account for the largest quantities I have ever seen in the human body, so that excessive formation as an explanation is unnecessary. I do not assert that it never occurs, but I have met with no proof of its occurrence, while all the phenomena of disease can be explained by the ordinary formation of uric acid, plus a certain quantity introduced in food (see fig. 73).

Had my own sufferings been due to formation they would have remained incurable, as I should have formed excess of uric acid on any diet. But the above mentioned figure negatives this, and I have been cured mainly by stopping introduction.

The late Sir W. Roberts says ("Urinary and Renal Diseases," ed. iv., p. 73): "It may be regarded as probable that the defective power of the kidneys to eliminate uric acid in gout arises from a diminished alkalescence of the blood."

From my point of view it has nothing to do with the kidneys; the urates are not in solution in the blood, nor are they brought to them; when they have been got into solution by an alkali and brought to the kidneys they are easily excreted.

But neither Sir A. Garrod nor Sir W. Roberts knew that the excretion of uric acid can be varied at any time and in any direction —a discovery which not only enabled me to explain the symptoms of the uric acid headache, but disclosed the way in which, by gradual accumulation of small quantities, large amounts of urate are eventually retained without excessive formation. I also learnt that the daily fluctuations in excretion of uric acid are due to the same cause, and depend on the amount of solvent alkali in the circulation; the greatest excretion of the day occurring in what Sir W. Roberts has called the "alkaline tide," and the smallest in the high acidity period of the night.

It is, indeed, easy to demonstrate that this large excretion in the "alkaline tide" is not due to formation; for if a dose of alkali is taken at bedtime for several nights, there is an increased excretion of uric acid during the night, and the "alkaline tide" excretion is correspondingly diminished till after a few days the hourly excretion is almost equal throughout the day and night.

I must express my respect for the work of Sir A. Garrod, which, founded as it is on accurate experimental research, will remain a landmark for all who work at uric acid.

And if in a few points I have ventured to give other explanations of the facts, or to think that in some few of his results he may have been misled by the working of a less perfect process than that used by me, this has never hindered my recognition of indebtedness to his careful records and valuable suggestions.

To Dr. Liveing's work on headache I owe, not only knowledge of the relationship of migraine to gout, but also that of migraine to epilepsy and of both to gout, and it was his quotation from du Bois Reymond and others which led me to look for a uric acid reaction in epilepsy, resembling that which I had found in migraine.

Since the first edition of this book (1892) I have made two discoveries with regard to causation of disease by uric acid. Firstly, that uric acid taken by the mouth passes into the blood, and that if the blood is kept in a condition to hold it in solution, it will remain there till the kidney has time to pass the whole of it into the urine; so that of 12 grs. taken by the mouth some 10 or 11 grs. can be obtained from the urine within three or four days after it has been

swallowed (see *Journal of Physiology*, vol. xv., p. 167). This emphasises two important points: (1) That the uric acid excreted normally in the urine comes from two sources, (α) the uric acid formed in the body from nitrogenous food and (β) the uric acid introduced in meat, meat extracts, soup, tea, coffee, &c., all of which contain it in considerable quantity. (2) That in so far as the morbid processes of which I speak are due to excess of uric acid in the blood, they can be produced by swallowing that substance, and thus any one can repeat my experiments.

As regards the quantity of uric acid in meat, meat extracts, soup, &c., the following points must be remembered.

Not to go deeply into theoretical chemistry, it may be said that Haycraft's process for the estimation of uric acid in urine, which I have used throughout, estimates as uric acid not only the uric acid present, but also a certain amount of xanthin, hypoxanthin, or other members of the xanthin group.

This process, therefore, estimates the amount of uric acid too high in proportion to the amount of the xanthin bodies present; but inasmuch as urine contains only very small quantities of them the error from this source, so long as the process is applied to urine, is not great.

Some writers speak of uric acid and the xanthin bodies not as the xanthin group but as the alloxur or purin group, according to the name of a chemical combination supposed to form its basis. I mention this that readers, unacquainted with later literature of the subject may not be confused by names which carry no new discoveries or changes in chemical formulæ.

As met with in human urine, uric acid contributes from four-fifths to five-sixths of the group, and the remaining one-fifth or one-sixth is composed of the xanthin bodies. I therefore call the group by the name of its chief constituent, other writers having one name for the whole, in which the well-known chief constituent is merged.

When the process is applied to extracts of muscle, blood and other tissues, which contain considerable quantities of xanthin bodies in addition to a little uric acid the error may be very large indeed, and what is reckoned as uric acid may not, chemically speaking, be that substance at all.

Were this a work on Physiological Chemistry, the error thus introduced would be serious. I shudder to think of the number of atoms of oxygen inadvertently added on to the xanthins contained in muscle by reckoning them as uric acid.

But as we are dealing with physiology and pathology alone, the chemical inaccuracy is negligable; indeed it has probably been an advantage, for it makes absolutely no difference to physiological and pathological results whether a man swallows two grains of hypoxanthin, xanthin, caffein, theobromin, or uric acid; all these substances alike producing obstructed capillaries, high blood pressure, headache, mental depression, scanty secretions, and large excretion of a substance estimated as uric acid in the urine by Haycraft's process.

If I had estimated only the true uric acid in muscle, I should have missed the explanation of its physiological and pathological effect, and we must not forget that my research originated with the observation that a certain form of headache is made worse by eating meat, meat soup, or meat extracts, and is cured or prevented by corresponding abstinence.

If physiological chemistry is correct, muscle contains a very small quantity of true uric acid, but a considerable quantity of xanthins which are physiologically and pathologically identical and differ from it chemically merely in the absence of one or more atoms of oxygen.

The explanation is therefore complete; meat produces the headache by introducing into the body and blood uric acid plus substances of the xanthin group, and the same headache and visible slowing of the capillary circulation can be produced by swallowing any of these in a state of comparative chemical purity.

In applying Haycraft's process to extracts of tissues I was walking on dangerous ground as regards theoretical chemistry; I therefore point out (ed. ii., p. 355) that, while I gave figures of the amount of uric acid found in various animal foods by this process, the only satisfactory test is the physiological one of eating a known quantity and watching the effects on excretion in the urine (see figures in chapter iii. and elsewhere). This can be done without any fear even of theoretical chemistry, for as xanthin, hypoxanthin, &c., have only been found as mere traces in urine, it follows that the relatively considerable quantities of these contained in meat food must be largely converted into uric acid by the addition of oxygen in their passage through the body.

With reference to the Haycraft process, in an extensive experience during the last twenty-one years, for at least eight or nine of which I used it incessantly (see chapter ii.), I found it a most accurate and satisfactory test, and when I compared it with

other processes, working on known solutions, I was convinced of its superiority.

Persons without a tithe of my experience have criticised it, but I can find no good ground for this.

I also wish to controvert the not infrequent statement that my results are unreliable because I use this process. It is mistaken for two reasons: (1) because this process is most accurate; (2) because, even if it were not so, my results are independent. Not only have the most important been verified by other workers using different processes, but it has for some time been possible to work directly on the blood to estimate the uric acid it contains. And yet the results obtained either by myself working direct on the blood, or by others with various processes agree completely with those previously obtained by the disputed Haycraft process.

My second discovery was that uric acid present in excess in the blood seriously affects its quality, producing the changes met with in anæmia, paroxysmal hæmoglobinuria and other diseases, and also counteracting the effects of iron and preventing it from building up the blood and curing these diseases (if indeed iron has any such action).

Thus I found not only that by administering uric acid I could control the value of the blood decimal (hæmoglobin divided by red cells) in myself and others, but that my own actually varies daily and hourly (see fig. 52) in accordance with the quantity of uric acid passing into the urine. It has been pointed out by other observers that the blood decimal is commonly high in the morning and low in the evening, a circumstance due to the fact that little uric acid passes through the blood at night and a good deal by day, as can be proved by making the uric acid of the night large and that of the day small, when the blood decimal is low in the morning and high in the evening, thus reversing its usual movement (see fig. 53). We shall also see that uric acid affects not only the blood, but in a similar way the function, nutrition, and eventually the structure of every organ and tissue, and as regards infectious diseases has, in some cases, a more important influence than the microbes themselves. In the tissues, it controls not only nutrition but also their great physiological functions (the production of energy and the production of heat) to an extent which, acting as it does from hour to hour throughout life, is of enormous importance.

Recent advances have carried us beyond this, and it is

apparent that uric acid controls and conditions the capillary circulation of the whole body (this control can be demonstrated in less than a minute, and without instruments), thus regulating the blood pressure, the heart's action, the nutrition of the heart and vessels, the nutrition of the tissues, and all the metabolic phenomena constituting the life of the body to its minutest cells.

For the granules precipitated in the blood by chloride of ammonium and first mentioned in the fourth edition, prove to be an absolutely certain guide to the quantity of uric acid in the blood and urine; corresponding with this in pathology, drug action and physiology, and under all times and conditions. So that with drugs it is possible to change the number of granules in the blood from a relation to the red cells of say 1 to 30 or 1—40 up to a relation of 1 to 5, 1 to 3, or even 1—1, and to do this at pleasure (see chapter iii.).

With this change in the number of granules in the blood, corresponding changes in the quantity of uric acid in the urine and in the capillary circulation of the whole body are invariable.

And the capillary circulation controls the blood pressure and the rate of the heart's action, and many other circulatory and metabolic phenomena dependent on these.

With a small number of granules in the blood 1—30 the capillary circulation is quick, so that C. R. (=Capillary Reflux, see chapter v.) is only 3—4 half seconds, the blood pressure is low, 100 mm. of mercury, and the heart's action is quick, above 72.

With a large number of granules in the blood, produced by drugs or due to physiological changes, diet or other natural causes, the capillary circulation is slow, so that C. R. is 8—10 or 12 half seconds, blood pressure is high, 140 mm. or above, and the heart's action is slow, 60 or below.

With the small number of granules in the blood and quick capillary circulation, low blood pressure and quick pulse, goes the pathological condition—fever.

With a large number of granules in the blood, slow capillary circulation, high blood pressure and slow pulse, goes the pathological condition—Bright's disease.

The one can be distinguished from the other with absolute certainty, and in less than half a minute, by gauging C. R. with the tip of the finger.

And all these phenomena, uric acid in blood and urine, blood granules, capillary circulation, blood pressure, and numerous conditions of nutrition dependent on capillary circulation and blood

pressure, not only always correspond, but can be changed at pleasure by drugs which have long been known to control the amount of uric acid in the urine.

Thus, any accurate measurement of capillary circulation or blood pressure and their results is a measure of the uric acid in the urine and blood, because this controls the circulation.

And we can not only say that meat produced the uric acid headache by introducing uric acid and xanthin into the body, but can demonstrate that every symptom was the effect of excess of uric acid on the capillary circulation, the blood pressure and the phenomena these control.

We can demonstrate also that the headache can be produced by swallowing either uric acid or any one of half a dozen forms of xanthin in known quantity, and that this and all its symptoms remain absent if the blood is kept in a state of physiological purity and freedom from uric acid (absolute freedom being, of course, impossible).

This relative freedom can be produced either by diet free from the poisonous xanthins of flesh and tea and similar substances (which is far the best way), or by drugs which clear the blood by forming insoluble compounds with uric acid while not aiding its elimination from the body, or by other drugs which clear the blood by elimination through the kidneys.

With this relative freedom, however produced, go free capillary circulation, quick C. R., and normal blood pressure; and the headache and its phenomena will be absent so long as the freedom of blood from excess of uric acid and granules is maintained.

I know no proof of the reality of any knowledge save its power of control, and my power over the uric acid headache and the determining circulation conditions is now little, if anything, short of absolute.

The uric acid headache being a functional circulatory disturbance is the epitome of a wide field in pathology, and knowledge of its causation increases our power over many diseases similarly connected with the circulation.

As several figures will demonstrate, power over the quality of the blood and its changes, both physiological and pathological, is now considerable; former readers will see that these powers have been enlarging for years, while those who have applied these statements to practice have, like myself, found that they possessed powers of control previously unknown.

To make these general statements as definite and clear as possible, I will give in tabular form an epitome of the changes in circulation phenomena and their results, that can be produced at will.

Let us take, say, a case of acute rheumatism before treatment by salicylates and after it (*i.e.*, 10—12 or 15—24 hours later).

ACUTE RHEUMATISM.

Before Treatment.	*Later after 60—90 or 120 grains of salicylate of soda.*
Temperature 102°.	Temperature 99°.
Pulse 110.	Pulse 70.
C. R. 3—4 half seconds.	C. R. 8—10 half seconds.
Blood pressure 80—90.	Blood pressure 110—120.
Urine per hour 50—70 cc.	Urine per hour 30—40 cc.
Uric acid to urea 1—40 to 1—50.	Uric acid to urea 1—15 to 1—12, even 1—10.
Uric acid per hour 0·3—0·4 grain.	Uric acid per hour 0·8—1·0 grain.
Blood granules to red cells 1—30.	Blood granules to red cells 1—3 to 1—5, or even 1—1.
Blood decimal ·55.	Blood decimal ·53.
Water from lungs, above normal.	Water from lungs, below normal.
Difference between temperatures in mouth and rectum 0·5 or less.	Difference between temperatures in mouth and rectum 1·0—2·0° or more.

These changes are not due to change of temperature and relief of acute pain, for salicylate produces identical, though less marked changes in a few hours in physiological conditions.

None of them are accidental or fortuitous, all are consecutive; if one is absent those dependent on it are also absent.

Thus the central factor is the uric acid in the blood as shown by the blood granules and excretion in the urine.

The secondary phenomena are capillary circulation, blood pressure, pulse rate, the quantity of water passed from the kidneys and lungs per hour, and the relation of surface to deep temperatures; and these are results of the free or blocked capillary circulation in various parts of the body to which they each bear witness. The circulation in the retina tells the same tale (see fig. 38).

If any condition prevents the salicylate from producing excess of granules in the blood, and of uric acid in the urine, the secondary phenomena will be absent.

The quantity of uric acid in the blood can therefore be measured by the C. R., with the point of the finger and the power of counting half seconds, or by

The blood pressure;

The pulse rate;

The water from the kidneys or the lungs, and doubtless also that from the skin and other glands;

The difference between surface and deep temperatures, as well as by the blood granules and the absolute and relative excretion of uric acid in the urine.

This is either knowledge or it is not; the question is not to be debated apart from the facts; but is one of power or failure of power to prevent and control disease by this means.

That I myself am alive and well to-day is a convincing demonstration to which similar experiences are constantly added. Eighteen years ago my blood pressure was at least 20—30 higher than at present, headaches were severe and frequent, and my blood decimal also was quite 20 per cent. lower than at present.

These facts can be demonstrated in from twelve to eighteen months on any sufferer from these forms of headache, by anyone who will record the conditions, before, during, and after treatment.

The point is that a man suffering from uric acid "disease" is excreting in the urine 16 to 18 grs. per day.

By altering diet to prevent introduction the uric acid excretion will, in eighteen to twenty-four months, have sunk to 10 or 11 grs. per day, and all the signs of excess of uric acid in the circulation and fibrous tissues (collæmia and arthritis) will disappear.

It is impossible to reduce uric acid below 10 or 11 grs. per day because this quantity is formed in the body in the relation to urea of 1 to 34, and varies with urea daily.

But as a rule this small quantity of uric acid (10 to 11 grs.) is excreted daily and does no harm; it is only the extra 6 to 8 grs. a day introduced with the food which is injurious; and if we control this introduction we control or prevent disease, and if it has not gone too far, cure it.

The C. R., the urinary water per hour, and the surface and deep temperatures can be recorded by anyone.

The blood pressure and the blood decimal are not difficult when the instruments are obtained (see chapter xviii.).

The blood granules are easy and the uric acid in the urine only wants a little practice.

The uric acid in the urine can be estimated by any reliable process and is independent of any one. It will be evident that many of my results have been corroborated by other workers with different processes.

For daily work C. R. and blood pressure with an occasional examination of the blood granules and the blood decimal are sufficient, and even with C. R. alone it is possible to tell with great accuracy what the uric acid is doing either hourly or daily (see figs. 38 to 43 and 75); in fact to see it passing through the blood.

The conclusion is, avoid unnecessary uric acid, and the "diseases" (really signs and symptoms of poisoning by it) will gradually disappear; this decides the question of causation, for exclusion of uric acid will either relieve or fail to relieve.

A practical answer above and beyond all theories can thus be had in from eighteen to twenty-four months or sooner.

CHAPTER II.

Formation and Excretion of Uric Acid.

An early observation on the excretion of uric acid and its relation to headache showed that while there might be a bad headache one day, with, say, an excretion of 16 grs. of uric acid in the twenty-four hours, an exactly similar excretion might occur on another day without any headache, and viewing only the absolute excretion of uric acid these observations appear contradictory.

It was necessary, however, to consider something besides the absolute excretion of uric acid, viz., its relation to urea, and immediately a difference between these two days was seen. When 16 grs. were excreted without a headache, the relation of uric acid to urea was 1—33 (one of uric acid to 33 of urea), but when, with a similar absolute excretion of uric acid there was a severe headache, its relation to urea was 1—18 or 1—20.

The uric acid excretion in the uric acid headache is not only large, but is greatly in excess of its normal relation to urea. Before going further let us try to determine the normal relation of uric acid to urea in excretion, and also if possible in formation.

My researches have extended over a large part of the last twenty-one years, but taking only the figures of the longer periods of my estimation of my own excretion, we get a total of 3,161 days in which 38,029 grs. of uric acid, 1,104,730 grs. of urea, and 158,723 grs. of acid (reckoned as oxalic acid) were excreted; giving a relation of uric acid to urea of about 1—29, and a relation of acid to urea of 1—6·9.

These figures divided by the number of days give uric acid 12 grs., urea 349 grs., and acidity 50 grs. per day. My urea at the present time runs at from 360 to 420 grs. per day, or from 3 to $3\frac{1}{2}$ grs. per pound, and the low urea in the totals just given is in part the result of my having attempted to diminish my nitrogen during several years included in the above totals (see fig. 73).

Knowing now that the uric acid which caused my troubles was principally due to introduction, I keep urea about the physiological level by eating substances which contain sufficient nitrogen, but introduce little or no uric acid or xanthin (see chapter xvii.).

The total uric acid is increased probably by about 200 grs. swallowed for experimental purposes, and, say, some 300 grs. stored in the body before the estimation of the excretion: (thus I have calculated, from the percentage of urate found in the various organs and tissues after death, multiplied by the weight of these tissues in the body, that a man of ordinary weight would probably have at least 300 grs. I have therefore put down 300 grs. as the quantity in my own tissues, but these calculations are provisional and subject to revision).

Subtracting the 500 grs. thus accounted for from the total of 38,029 grs., we get 37,529 grs. as representing the excretion of uric acid in the above 3,161 days, apart from the urate intentionally introduced, and from that already present in the body when the experiment began. This gives a daily excretion of nearly 11·2 grs. of uric acid and a relation of uric acid to urea of about 1—31·1.

But daily excretion equals daily formation plus the daily introduction of urate ready formed in the food, and though my food is probably much poorer in urate than that of persons with an ordinary allowance of butcher's meat, soups and meat extracts, still there seems little doubt that it contains some uric acid or equivalent members of the xanthin group. Let us say that I introduced during some periods of my research with my food 1·2 grs. of uric acid per day; subtracting this from the 11·2 grs. of daily excretion we get 10 grs. of uric acid as the actual quantity daily produced out of nitrogen introduced in other forms, the remainder of this nitrogen furnishing about 349 grs. of urea, giving a relation of uric acid to urea of 1—34.

Now that pulses are removed from the diet (see chapter xvii. and fig. 75), daily introduction is probably a mere fraction of a grain; but as we can only say that formation is about 1 to 34 we can only estimate introduction roughly by the difference between 1 to 34 and the actual daily excretion; nor are we certain that some of that difference may not be due to solution of previous storage.

Let us work out the formation and excretion of a man of 150 lbs. from these data. Say that he forms 3·5 grs. per lb. of urea = 525 grs. a day, and uric acid in relation of 1—35 = 15 grs. per day. He will introduce in his food perhaps 1 gr. of uric acid per 100 grs. of urea = 5·25 grs. Therefore the total uric acid formed and

introduced will be 20·25 grs. a day, and if he excretes the whole of this it will hold the relation to urea of 1—26. But with higher introduction of uric acid diminished alkalinity of blood will result and, depending upon it, lessened solubility and excretion of uric acid; that is to say, he will not excrete all the uric acid introduced or formed, but will retain a portion. So that while I, in 3,161 days, have probably washed out of my tissues and excreted some 300 grs. of uric acid because acidity has been low, this man with higher acidity may have retained in the same or a shorter period some 300—400 grs.

Such a man, instead of excreting the full 20·25 grs. of uric acid formed and introduced each day, will only excrete, say, 19·5—20·0 grs., retaining the remaining ·2—·7 of a grain, which in the course of years will amount to many hundreds of grains, and the higher the acidity the greater the proportionate retention.

I consider that every man on ordinary diet, who also drinks acid wines or beer, will by the time he is 50, have accumulated 300—400 grs. of uric acid in his tissues, and possibly much more; and about this time he will probably be subject to attacks of some form of gout or chronic rheumatism and will have defective capillary circulation and a low blood decimal.

If he is killed by accident uric acid more or less equivalent to the above-mentioned amounts, will be found in his tissues. If he dies after several years of wasting disease much less appears, for during his wasting there will be a marked fall of urea and acidity, his blood will become more alkaline and will take up uric acid from the tissues and pass it in excess in the urine. Hence we find erosions with little urate deposit in the joints of patients who have died of wasting disease, though before they began to waste the erosions were doubtless full of it.

If the blood of such a patient is examined periodically a steady and continuous fall of the blood decimal (see chapter xii.) will appear corresponding to the amount of uric acid passing through the circulation, and this is no doubt the causation of much anæmia of old age.

In most cases of wasting disease the plus excretion of uric acid and excess passing through the blood produce recognisable symptoms such as slow capillary reflux (see chapter v.), slow high tension pulse, with some headache and mental depression, and I doubt not that in the more or less physiological conditions of old age excess of uric acid in the blood, with similar causation, plays an important part.

With regard to the relation of uric acid to urea in excretion, namely, 1—33 to 1—35, other investigators, Yvon and Berlioz (*Rev. de Med.*, September, 1888), found as the result of one series of experiments the relation 1—30, and of another series 1—40: while Lecanu (quoted by Sir Dyce Duckworth, "A Treatise on Gout," p. 120) found much the same relation as my own, viz., 1—33.

There is thus a considerable collection of figures tending to show the normal relation of uric acid to urea in excretion, as 1—30 or thereabouts, and I suggest that where this is found over a long period of time, it may represent something near the real relative formation of the two. It is probable, however, that these results all include a considerable quantity of exogenous uric acid, so that the ratio of formation in man may be nearer 1 of uric acid for 35 of urea (see also Pulses and Researches on them in chapter xvii. and fig. 75).

I agree with Sir A. Garrod, that the final stage in the formation of uric acid is the production of urate of ammonium in the kidney.*

According to this theory a large part of the urate so formed passes at once down the ureter and is excreted, but a residue lingers in the kidney or the blood circulating in it and is eventually carried by the renal vein into the general circulation, where it is, according to the same authority, attracted differently by different organs, rendered less soluble and so retained and accumulated in such organs as the liver, spleen, and certain fibrous tissues especially those of joints, probably because these are less alkaline than other tissues and fluids.

These theories of Sir A. Garrod enable me to explain my results regarding the excretion of uric acid—not to mention a whole string of disease processes of which they afford an equally simple explanation.

We may now return to our original question—why there is a headache one day with an excretion of 16 grs. of uric acid, and little or no headache another day, when an identical quantity is excreted.

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* Sir A. Garrod read a paper before the Royal Society, in 1893, in which he shows that there is urea in the blood of birds though their urine contains none. He concludes, I believe, that in birds, just as in man, uric acid is formed in the kidney out of urea and other nitrogenous antecedents furnished in the blood.

Allowing that uric acid is never formed in greater relative proportion to urea than 1—33 (1 gr. uric acid for 33 grs. of urea), how comes it that on any given day uric acid is excreted in the relation to urea of 1—18 or 1—20?

Obviously Sir A. Garrod's theories supply an explanation. If 16 grs. of uric acid are excreted, while (judging from the urea excreted) only 12 grs. of uric acid were formed, then 4 grs. of uric acid must have come from elsewhere, *i.e.*, must have been formed on some day when they were not excreted but were retained—in the liver, spleen, joints, or fibrous tissues.

The curves I have shown to illustrate various papers bear this out. In my paper on "Headache," in the *Transactions of the Royal Medical and Chirurgical Society*, I mentioned that the excess of uric acid on the day of headache was almost exactly accounted for by the amount retained, as shown by the curve on the four or five preceding days (see fig. 45).

In so far as the headache was due to uric acid, therefore, it was due to a fluctuation in excretion, no alteration in formation having necessarily taken place, and the action of various drugs bears out this supposition.

When 16 grs. of uric acid were excreted with 528 grs. of urea (*i.e.*, in the nearly natural relation of formation 1—33), the whole 16 grs. of uric acid were formed that day in the kidney, and no headache followed because there was no great excess of uric acid in the blood.

When, however, 16 grs. of uric acid were excreted with only 396 grs. of urea, a relation of 1—24·7, the whole of the uric acid was not formed in the kidney on this day, and some 4 grs. of it must have come from other parts in which we suppose it to have been retained.

This uric acid, however, traverses the blood in addition to that usually overflowing from the kidney; it would be for some hours in excess, and would give rise to headache and other signs of its presence, which is, I think, a sufficient answer.

Similarly any exogenous uric acid will pass through the blood on its way to the kidneys, and concomitant conditions reveal from which source (introduction or retention) the excessive excretion proceeds.

The relation of uric acid to urea in excretion is therefore of great importance, as it shows on any given day whether there has or has not been an excess of uric acid in the blood, and the condition of the blood, its hæmoglobin value or its circulation, from hour to hour or day to day, can be used as a further index.

I remind my readers that if one grain of uric acid is held back in the body daily, nearly one ounce could be so provided in a year, and though this is rare, the balance of retention and excretion over a series of years may tend either to increase the stores or to diminish them.

Fig. 1 shows the natural plus excretion of uric acid which occurs daily during certain hours.

The exact hours depend upon habits of food, exercise, sleep, &c., because these control daily fluctuations in acidity, and acidity

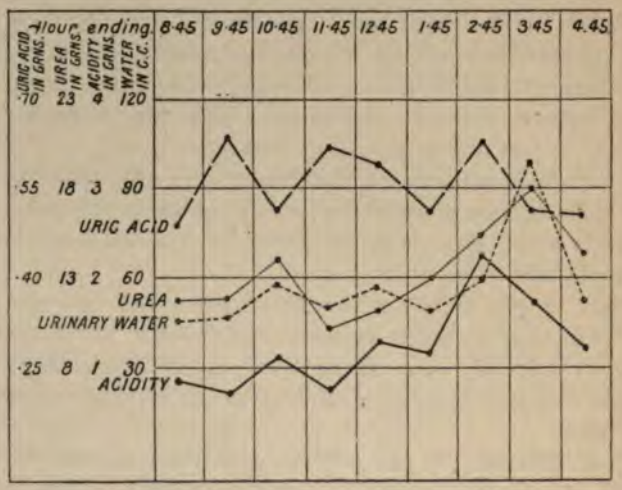

FIG. 1.—NATURAL PLUS EXCRETION OF URIC ACID IN THE ALKALINE TIDE.

Breakfast ended 9.50 A.M. Lunch ended 2.10 P.M. Two and a half miles sharp walking 3.0 to 3.45 P.M.; perspiration, and low tension pulse after walk. Total urinary water 527 cubic centimetres. Total urea 118 grains. Total uric acid 5·0 grains. Relation of uric acid to urea 1 to 23·6.

controls excretion of uric acid. By altering the acidity of the whole day we alter the excretion of uric acid also.

In this figure we see that the curve of acidity is low at 8.45 a.m., and rises gradually up to 2.45 p.m.; after this it drops, more or less decidedly, producing what I call the second or afternoon alkaline tide.

As a result of this low acidity in the a.m. and early p.m. hours, uric acid is above urea, and comes below it for the first time at 3.45 p.m.

We must bear in mind, however, that this high uric acid depends upon two factors—(1) the low acidity of the urine corresponding to high alkalinity of the blood and rendering that fluid a good solvent of uric acid, and (2) the presence in the body of a quantity of uric acid available when the condition of the blood is favourable for solution.

If available uric acid has been cleared out by means of solvents acidity may fall much lower than in this figure without any plus excretion (see fig. 73).

It is of the first importance to bear the above-mentioned factors in mind if we are to avoid misunderstanding in watching the daily and hourly excretion.

We see also in this figure that urinary water is low all through the morning hours and rises for the first time at 3.45 p.m., when for the first time uric acid is below urea.

So that it, like many others in this volume, illustrates the relation between uric acid and water in excretion which I have ventured to formulate as a law—that urinary water varies hourly and daily, inversely with the excretion of uric acid or with the height of the uric acid above urea.

We shall see that other secretions and excretions bear a similar relation to the amount of uric acid in the urine and blood, that this is of the utmost importance in demonstrating the power of uric acid over the circulation, and that the capillary circulation and blood pressure bear a similar relation to uric acid excretion. So that a touch with the point of the finger will reveal in the slow or quick capillary reflux whether we have to deal with scanty urine or diuresis, with free excretion of water or dropsical retention; for dropsy is nothing but a result of retention of water in the body due to collæmia, generally acting in association with more or less heart failure and cutting off all excretions.

Figure 2 shows the daily excretion of uric acid, urea, water and acidity in epitome.

The total excretions of the hours placed at the top of each column are divided by the number of hours, so that the curves represent the average hourly excretion in each period.

We see that in the hours 7 a.m. to 11 p.m. (*i.e.*, the usual working day hours) uric acid is above urea, and water is low. Acidity is also low, and hence the cause of high uric acid.

In the hours 11 p.m. to 4 a.m. acidity and urea have risen considerably; as a result of the high acidity uric acid has fallen below urea, and in consequence of this low uric acid (which

means absence or relative absence of uric acid from the blood), the capillaries are freed and there is free elimination of water from the blood and a diuresis; hence the urinary water is very high.

The free capillaries produce everywhere definite effects, with some of which I deal later, and it will then appear that part of the rise of urea is due to the fall of uric acid and to the free capillaries and increased metabolism resulting from this fall.

In the hours 4 a.m. to 7 a.m. acidity falls to its lowest point, urea falls very greatly, water drops also to its lowest point, and uric acid rises.

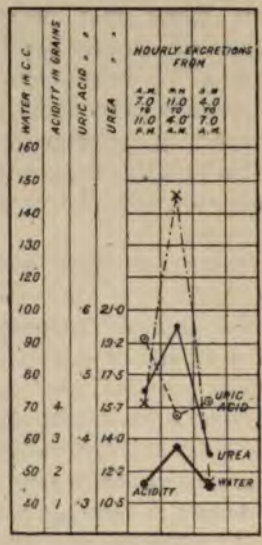

FIG. 2.—DAILY EXCRETION OF URIC ACID IN EPITOME.

The rise of uric acid is due to the fall of acidity, but also to the retention in the previous night hours.

When uric acid was low in the night there was no alteration in its formation relative to urea; it was formed then as always in the relation to urea of about 1 to 35, but the condition of the blood not favouring solubility, a certain quantity was retained in some of the organs and tissues, and therefore the moment acidity fell in the early morning hours this available uric acid passing into the blood and urine raised the excretion of uric acid above urea, there being again no alteration in formation (relative to urea).

This is susceptible of simple demonstration, for if you administer sufficient alkali to prevent the rise of acidity in the night, there is no excess of uric acid passed in the urine of the early morning hours.

Whereas if the large excretion in the morning were due to new formation of uric acid it is difficult to see how the previous administration of an alkali could prevent this.

Further, if an alkali were given to prevent rise of acidity and fall of uric acid in the night hours, there would be no diuresis; the water would remain in the blood and body and pass out next day whenever uric acid was exhausted and fell close to urea from this cause.

I ask my readers to bear this small figure in mind as the key to nearly everything that follows. They will find that by controlling acidity or uric acid and producing changes in these (such as are shown in the figure), they can control to a large extent urea and to a still greater extent the urinary water, and these are the signs and results of more important control over the capillaries, blood pressure, action of the heart, and physiology of the whole body.

Now the acidity is controlled by administration of acids and alkalies, by increase or diminution of activity and perspiration (as in fig. 1), or by altered formation of urea (as in fig. 2), and many things indirectly affecting these factors.

Uric acid is controlled by the administration of many substances increasing or diminishing its solubility in the blood; it is also increased by direct administration of uric acid itself or of xanthin or many xanthin compounds practically equivalent.

In making any such experiment, it is necessary to remember that the alterations in the curves of fig. 2 represent the resultants of a large number of forces acting variously, and that whatever substance is used to produce a given change must be in sufficient quantity to overcome other and opposing forces.

Fig. 3 shows much the same thing. It gives the actual hour to hour excretions of the working day but it was obviously impossible to divide the night without interfering so much with physiological conditions as to invalidate results, and I had, therefore, to take chance divisions. I have also added the result of dividing the whole day's excretions by 24 so as to make it comparable to the hourly excretions and give an average by which to judge them.

We see, then, much as in fig. 1, that uric acid is above urea all

the morning hours and does not come below it till 3 p.m., and that with the exception of 8 and 9 p.m., and the early a.m. hours of the following day, it is below it during the rest of the twenty-four hours.

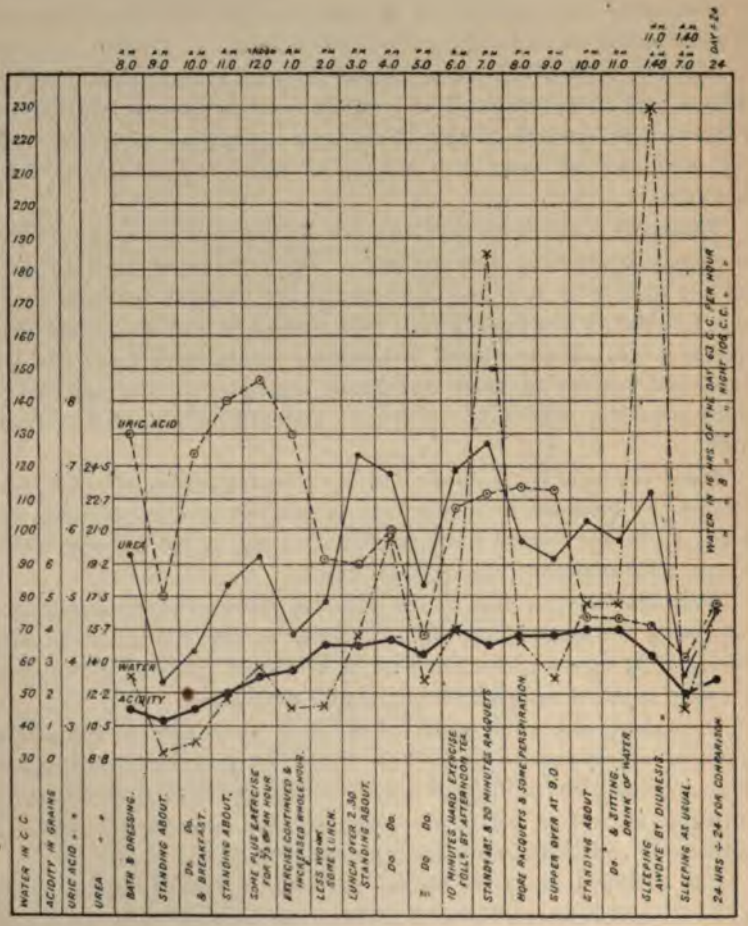

FIG. 3.—DAILY EXCRETION OF URIC ACID FROM HOUR TO HOUR.

The average hourly excretion of uric acid is below ·5 of a grain or less than 12 grains in twenty-four hours, the highest hourly excretion about ·8 grs., and the lowest little above ·4.

Acidity and urea run fairly well together though urea fluctuates much more than acidity. They agree in being low in the morning

hours and high in the afternoon, evening, and early part of the night.

The relation of acidity to urea is fairly constant over a long period of time at about 1 of acidity for 6·8 of urea, and I attribute this to their being two results of the same metabolism; that is to say, that every molecule of proteid material which in breaking up furnishes the constituents of urea, furnishes also certain acids, salts, or substances capable of oxidation affecting the acidity of the urine. For instance, sulphur in several forms is capable of oxidation in the body, as its administration always raises the acidity of the urine (see fig. 11).

The average acidity is about 2·5 grs. per hour or 60 grs. a day.

The highest acidity is at 6, 10, and 11 p.m., when it touches 4 grs. per hour; and the lowest at 9 a.m., when it is little above 1 gr. per hour.

The acidity changes determine the excretion of uric acid, which is above urea when acidity is low and below or close to urea when it is high, and the amount retained each day when it is below urea, furnishes the excess excreted next morning when it is above; therefore any unusually large retention on the evening of one day is followed (other things equal) by an unusually large excretion next morning.

The quantity excreted from 8 a.m. to 2 p.m. in this figure is partly the result of the low acidity which aids its solution, and partly of the uric acid retained on the previous evening which furnishes the supply, and the amount by which uric acid exceeds urea on any given morning depends chiefly on these two factors.

The average excretion of urea is about 16 gr. per hour, or 384 grs. per day, and it fluctuates from a maximum of about 25 grs. per hour to a minimum of about 13 grs. per hour at 9 a.m. It appears to rise soon after each meal and to fall decidedly in the early morning hours when food supplies are running short, probably causing the low acidity of these hours.

Uric acid on this day bears a relation to urea of 1 to 32, which is near normal if the uric acid is provided both by formation and introduction; had it been provided by formation alone it would have been nearer 1 to 34.

The average excretion of water is about 75 cc. per hour, or 1,800 cc. per day, but varies enormously from a maximum of 230 cc. per hour between 11 p.m. and 1,40 a.m. to a minimum of about 33 cc. at 9 a.m.

The water is remarkably low through the morning hours and up

to 3 or 4 p.m., in spite of the fact that more than a pint of fluid is taken at breakfast.

No doubt this low water is partly due to loss by diuresis in the previous evening and night; but more largely to retention of water owing to the renal capillaries being obstructed by excess of uric acid.

Similarly the remarkable rise of water in the evening and night is due to excess of water in the blood, where it has accumulated during the morning hours, and also to the free action of the renal capillaries when the blood is cleared of uric acid; while, with regard to the great diuresis of the night, uric acid is further below urea in these hours and those just precedent than at any other of the twenty-four.

My law of excretions is thus fully illustrated, and the more minutely we investigate the better it shows that urinary water is inversely as uric acid and especially inversely as the height of uric acid above urea.

And we have seen that the height of the uric acid above urea is the measure of the quantity of uric acid traversing the blood in any given hour.

It may be said that water is scanty in the morning because there is none available and the blood is poor in water, but it is easy to disprove this suggestion. First examine the blood and you will find that it is dilute, *i.e.*, both cells and hæmoglobin are relatively scanty in a given quantity.

Having done this say at 9 a.m., give a drug to bring down uric acid, such as opium, calomel (or many others to be mentioned), and as soon as uric acid is brought to or below urea, you will get a diuresis perhaps as large as that at 7 p.m. Some of my results were very striking, and proved that the urine in these hours was not scanty from want of water in the blood.

Control uric acid and the water is invariably controlled, whether by raising acidity, or by giving a drug such as one of the metals directly forming an insoluble compound with it; if uric acid comes down water will rise, provided there is water available for excretion.

Conversely if uric acid is raised by a solvent the water will fall and will not rise again till uric acid comes down.

In disease the same law obtains. The onset of fever is accompanied by a rise of urea and acidity, and uric acid falls and is retained and a more or less marked diuresis results. I nearly always know when my temperature rises by the diuresis which

marks the onset of the rise. (For effects of fever on the capillaries of the skin and retina see fig. 42.)

Still more is this the case when fever follows dropsy, for there is a large supply of water available and if the fever continues this will last till many pounds of water have been run off, proving conclusively that the scanty urine often following the onset of a fever is due to lack of water and not to obstructed capillaries.

When the fever ends urea and acidity fall. The uric acid retained during the early stages of the fever is again got into solution, and a scanty excretion of water follows in spite of plenty in the blood.

Here we have the parallel in pathology of what occurs daily in physiology; uric acid retained during the high acidity of the fever passes out when acidity falls at its conclusion, just as uric acid retained in the evening and night when acidity is high passes out next morning when it is low.

And the diurnal variations in blood pressure with those which correspond to fever and convalescence are absolutely dependent on the uric acid.

Chronic Bright's disease provides another illustration. During the day there is excess of uric acid in the blood as shown by numerous granules (see chapter iii.) with obstructed capillaries and high blood pressure, and despite the ingestion of, it may be, large quantities of water, the urine is scanty but the blood is dilute. Such urine may have quite a good sp. gr., and the fact that it is the product of chronic Bright's disease may thus be overlooked.

In the night, however, this is reversed; with a rise of acidity, lessened quantity of uric acid in the blood and comparatively free capillaries, so great a diuresis occurs that the urine of the whole twenty-four hours is profuse and of low specific gravity, and under these conditions the hourly excretion of water at night is often more than twice as large as in the day.

Before leaving fig. 3 I will point out a way in which it may be misread.

Remembering that urinary water is inversely as the height of uric acid above urea—suppose we take three hours, such as 7, 8, and 9 p.m., and mix the urines, and suppose that uric acid as at 8 and 9 was not only above urea but was rather higher above it than in this figure, the mixing of these urines might result in showing a considerably greater excretion of water than in several of the morning hours, and yet uric acid might come out above urea. It might therefore be said, "Here is an exception to your law."

But when the hours are separated carefully it appears that the diuresis really occurred when uric acid was below urea, and in the following hours when it was above, the water was scanty, but the diuresis of the first hour was so great that it made the urine of the whole three hours seem profuse. There is no exception to my law; the more carefully it is investigated the more evident is its truth.

Conversely without water there can be no diuresis however much uric acid is brought down, and the capillaries freed; if the water has been run off by perspiration, vomiting, or diarrhœa there will be no diuresis till fresh supplies are available.

I do not claim that fig. 3 represents a typical day, it is one of many taken more or less at random from my researches, and details vary with diet, clothing, temperature, exercise, and other things: but the main points, that uric acid is above urea in certain hours and below it in others, that acidity is high in certain hours and low in others, and that the water varies inversely as the height of uric acid above urea, are practically constant for my excretions and those of everyone living under similar conditions. And this not only in physiology but for the most part also in pathology, dominating the circulation and consequently governing the nutrition and function of the body, probably from development and intrauterine life to the hour of death.

There is another point of interest in connection with fig. 3, and that is that when, as here, urinary water is scanty in the morning hours from obstructed capillaries and not from want of water in the blood, there is a distaste for fluids; whereas, after a diuresis when the blood is poor in water there is thirst, so that by observation it is possible to tell whether the scanty urine is due to collæmia* and obstructed capillaries, or to want of water in the blood.

In the morning hours the drinking of a considerable amount of water will not produce a diuresis; it is kept in the blood by the obstructed capillaries; in the evening and night it tends to pass soon after it is swallowed, and the same in the morning if the capillaries are freed. No doubt water is required for

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* Collæmia means excess of uric acid in the blood, the uric acid being in some colloid form which obstructs more or less the capillary circulation all over the body. High blood pressure is almost always due to collæmia, and the slowness of the capillary reflux and the height of the blood pressure are, other things equal, a measure of the extent of the collæmia. (See chapters v. and xvii.)

digestion, and while digestion is active a certain amount will be retained, but this takes place both in the morning and evening, and yet water is profuse in one and scanty in the other. If uric acid is removed so that there is no plus excretion in the morning the water will be passed freely as at other times, and in these circumstances there will be no great diuresis the following evening or night, because water has not been retained during the day.

The afternoon alkaline tide is poorly represented in fig. 3 by a small fall of acidity at 5 p.m., but this varies with exercise, food and other factors, and I believe is commonly due to the fall of urea as the albumens of lunch come to an end and to the alkaline bases introduced, aided by a certain amount of exercise commonly taken afterwards which tends to reduce the acidity by loss of acids in perspiration (see 3.45 and 4.45 in fig. 1); in the day represented in fig. 3 there was no exercise after lunch.

The diurnal variations in the excretion of uric acid explain absolutely the incidence of the related diseases.

Thus the diseases caused by excess of uric acid in the blood, headache, epilepsy, mental depression, melancholia and suicide, vertigo, high blood pressure, angina, asthma, Raynaud's disease, all tend to appear or to be worst in the morning hours, though, when there is any severe disturbance of digestion, there may be collæmia at other hours because the natural curve of acidity is upset.

Those diseases due to the presence of uric acid outside the blood, gout, rheumatism, and inflammations of fibrous tissues, affect especially the hours in which the blood is generally cleared of uric acid, *i.e.*, the evening and night, and illustrations will be found in the chapters treating each disease.

The diurnal fluctuation in the blood decimal corresponds well with those of acidity and uric acid in fig. 3; it falls in the morning with low acidity and high uric acid and rises towards 1 or 2 p.m. as acidity rises and uric acid falls; it drops more or less decidedly with the fall of acidity in the afternoon alkaline tide, varying with the distribution of meals and other factors, and rises decidedly in the evening and early night hours. The curves in fig. 52 only illustrate this partially, but this is a somewhat exceptional curve both as to uric acid and the blood decimal, and is given for reasons appearing in its description.

Fig. 4 is an attempt to show the annual fluctuations in the excretion of uric acid. I have no exact curves, because I have

taken so many drugs that the natural fluctuations have been more or less disturbed by their effects, and I choose this year simply because it seemed less obscured than others.

This figure discloses, speaking generally, that the warm months of the year correspond to the morning hours in displaying a relatively large excretion of uric acid, and this should be so for acidity

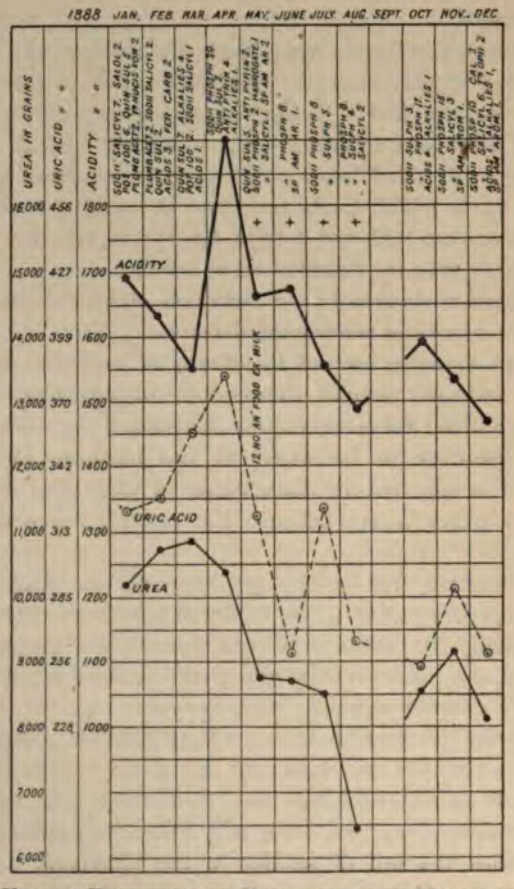

FIG. 4.—YEARLY EXCRETION OF URIC ACID FROM MONTH TO MONTH.

is diminished in them all by an increased loss of acids from the skin in perspiration, whilst the cold months of the year correspond to the evening and night hours and in them the acidity is raised by a diminished loss of acids from the skin, and with this a diminished excretion of uric acid.

In the cold months, October, November, December, January, and February, uric acid is nearer urea than at any other time with the exception of June.

With the fall of acidity in March uric acid rises.

The high acidity in April, May, June, July and August is due to drugs, and the numbers opposite these indicate the number of days on which they were taken.

May, June, July and August marked + were not estimated throughout, but the excretion for the month was estimated from the days worked out.

In many months a considerable quantity of phosphate of soda and sometimes salicylate of soda were taken and these tend to raise the acidity and also the excretion of uric acid, acting as solvents of uric acid.

In fact this year is selected because drugs are used so constantly that their effects may to some extent be neglected.

But with or without, the fact remains that acidity tends to be high in the cold months and low in the warm, and uric acid in its inverse relation to this tends to be low in the cold months and high in the warm. It follows from diurnal experiences that uric acid will tend to be highest in the early warm months, March, April and May (and this may account for part of its fall in June, unless, indeed, June was a cold month in 1888, which my notes do not enable me to say), and lowest at the first onset of cold, as in October.

The fall of urea from March to May was due to leaving off meat, and the further fall May to August was due to making milk my only animal food without due care in replacing the nitrogen thus dropped, an experiment I advise no one to repeat. Had I understood the direct introduction of uric acid it would have been unnecessary; but I then believed that my only way of reducing uric acid was to reduce the total nitrogen.

Taking these as the natural annual variations in the excretion of uric acid (and the whole of my researches and observations are in favour of this, as I discovered that I got a relatively increased excretion of uric acid 1 to 29, or 1 to 30 in the spring and summer months, as compared with 1 to 33 in the winter), it follows that the amount of uric acid excretion in the warm months will, as in the corresponding diurnal variations, depend partly on the greatness of the fall in acidity and partly on the quantity of uric acid stored in the cold months. A man who has introduced through the winter some 6 grs. of uric acid daily, ought to

suffer more severely from spring and summer diseases due to excess of uric acid in the blood than the man who introduces from 1 to 2 grs. per day, for he who introduces 6 grs. a day not only does so but the uric acid taken hinders its own excretion by tending to keep up the acidity of the urine and diminish the alkalinity of the blood, though if introduction is continued in summer it will tend to keep up the acidity then also. This, however, will have little effect compared to the external temperature, and whenever acidity is reduced there will be a rush of urates into the blood.

All diseases which in the diurnal variation of excretion exhibit their greatest incidence and severity in the morning, tend also to their greatest annual incidence in the spring and summer months, while those most prominent in the evening and night are most prominent in autumn and winter. I must add to the diseases which are worse in the morning hours, others such as phthisis, some skin diseases, and pneumonia, because though they are not of such a nature as to indicate their relation to the diurnal fluctuations of uric acid, some of them show a distinct relation to its annual fluctuations.

For the same reasons the blood decimal of the flesh and tea taker is higher in the winter months, as ·5 to ·55, and lower in the summer months, as ·45 to ·5; but at no time are the blood decimal or capillary reflux of the flesh eater equal to those of the abstainer, and consequently the flesh eater is never equal in endurance and athletic power.

It will surprise some to see such diseases as phthisis and pneumonia included, but uric acid, by controlling metabolism and combustion and such troubles as chronic catarrh, and inflammation of mucous membranes, in many instances determines whether microbes should be destroyed or live, and thus practically decides the incidence and course of microbic diseases. Moreover (chapters ix. and xvii.), uric acid, by affecting the fibrous tissues of the trachea and bronchi, not only produces acute inflammation of these structures but also causes pneumonia of neighbouring portions of the lungs and in any of these lesions bacilli and other microbes may find a nidus. In these cases uric acid is the factor the removal of which prevents or cures the disease; the microbe merely flourishes in the conditions which uric acid produces and is in itself unimportant (see cases under Catarrh, Pneumonia, Malaria, &c.).

Fig. 5 shows, I think, that the diurnal variations in the excretion of uric acid have an important effect on temperature.

This figure is one of a large number and I give it while the diurnal variations in the excretion of uric acid are fresh in our minds, though I must return to its points in connection with other subjects later.

The upper curve gives the rectal temperature, the lower curve that in the mouth.

It is noticeable that between the hours of 7 a.m. and 6 p.m. these temperatures are further apart than at other times of the day.

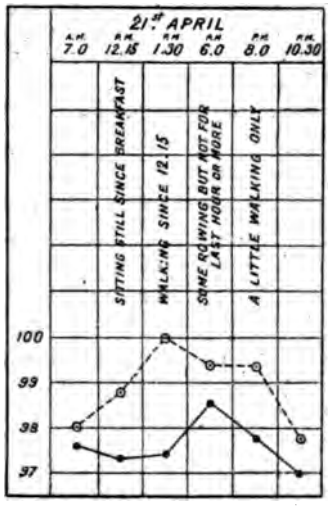

FIG. 5.—CURVES OF TEMPERATURE IN MOUTH AND RECTUM TO SHOW THEIR RELATION TO THE EXCRETION OF URIC ACID.

I was led to this investigation by some statements in Marey's work on the circulation of the blood ("Circulation du Sang," pp. 588 to 596).

He points out that by observing the temperature simultaneously in rectum and mouth we can distinguish whether a low temperature in the mouth is due (1) to contraction of surface vessels, or (2) to diminished production of heat.

If to contraction of surface vessels, the rectal temperature rises as the mouth temperature falls, and the two are far apart; if to diminished production of heat, the two will be close together.

Again, suppose we find a raised temperature in the rectum, if the temperature in the mouth is near it there is increased formation of heat, but if they are far apart, the mouth being lower, there is contraction (obstruction) of skin vessels.

Marey points out that in cholera algide rectal temperature is high in proportion as surface temperature is low, and in the reaction rectal temperature falls as surface temperature rises.

In cholera algide the surface vessels are contracted (? obstructed), and tartarate of antimony and emetine produce similar results.

Alcohol dilates the surface vessels and reduces the temperature in the rectum.

Inanition lowers the temperature both of surface and rectum, hence the diagnosis between this and contracted arterioles, or rather obstructed capillaries (see chapter v.).

In uræmia he states that a fall of the central temperature as well as of the surface may occur, *i.e.*, I suppose, the obstruction of vessels is so great and general that the production of heat is affected as well as its distribution.

During fever the two curves meet as the vessels are free, and the temperature equalised.

In cases of intermittent fever the curves are close and there is increased production of heat at times of high fever, but the surface temperature is considerably lower in the intervals and this corresponds with the amount of uric acid in the blood, this being absent during the fever, stored up in the enlarging spleen, in the liver and elsewhere, and present in varying quantity during the intervals.

This suggested that if the difference between the temperature of mouth and rectum is a measure of the obstruction of the skin-vessels, it might also be a measure of the amount of uric acid in the blood, for this obstructs the skin-vessels; on carefully investigating the point I found, as fig. 5 shows, that it is the case, and that the greatest divergence of these temperatures corresponds with the hours in which the largest amount of uric acid passes through the blood.

In this figure at 7 a.m. the two curves are pretty close together, and temperature was taken in bed, so that any effect uric acid might have on the skin-vessels was counteracted by the equable temperature of the bed clothes, and this is practically a constant feature.

The next observation is at 12.15 p.m., and here mouth temperature has fallen, while the rectal has risen, so that they are

considerably further apart than at 7 a.m., and the skin-vessels are therefore obstructed.

At 1.30 p.m. mouth temperature has risen slightly, the rectal considerably, and they are now 2½ degrees apart.

An hour and a quarter of walking exercise has raised the temperature, but has affected the rectal temperature much more than the mouth as the surface vessels are still obstructed.

At 6 p.m. the mouth temperature has reached its highest point; rectal temperature has fallen and approaches it and they are now only separated by about $\frac{8}{10}$ of a degree; the surface vessels are therefore little obstructed, and the alkaline tide, with the accompanying collæmia has ended.

At 8 p.m. rectal temperature remains the same as at 6, while mouth temperature has fallen. They are about 1½ degrees apart and the surface vessels are again a little obstructed; possibly there was a slight excess of uric acid passing through the blood as at 8 and 9 p.m. in fig. 3, but at 10.30 p.m. this has ended. Mouth temperature has fallen to its lowest point, but rectal temperature still more and is again close to it; the skin vessels are little obstructed, the blood is probably fairly clear of uric acid and this fall is therefore due to diminished formation of heat.

I have many curves showing almost the same thing. When there is no exercise to cause fluctuations the greatest divergence always occurs about 1 p.m., and the temperatures approach early in the afternoon, remaining more or less close in the evening and night.

The effect of exercise is interesting for it causes divergence of the two curves most in the morning but considerably also in the afternoon, and increases the excretion of uric acid passing a larger quantity of it through the blood. In accordance with its effects on uric acid, exercise controls formation and excretion of urea; these temperature curves show that uric acid controls the distribution of heat, and reason will be given later for believing that it also controls heat formation.

In the same way collæmia accounts for the algide stage of cholera, this being the natural result of every severe gastro-intestinal disturbance. Tartarate of antimony, emetine or sea-sickness produce the same result.

Alcohol, on the other hand (or the acids so often mixed with it), cures or prevents collæmia, it consequently frees the skin vessels and the temperature curves approach each other. I believe every drug thus affecting uric acid has the same effect on the curves.

In uræmia, which is merely severe collæmia, the obstruction of vessels may be so great that there is diminished production of heat, just as in severe fatigue there is diminished production of urea.

If the effect of uric acid is so great in the physiological conditions obtaining in fig. 5, its effects in pathology must often be much greater, and I believe this is certainly the case.

It is clear that in thus observing the superficial and deep temperatures and their co-ordination, we can readily estimate the amount of uric acid passing through the blood at a time when it might be impossible to estimate directly the quantity either in the blood or the urine, and can control our results by the use of drugs known to influence the solubility of uric acid and therefore the temperatures. The capillary reflux or blood pressure will reveal the same thing more quickly.

A uric acid headache affects the relation of these temperatures; thus in fig. 5 at 10.30 p.m. they are less than a degree apart, but if there is even slight headache at this hour they will be a full degree apart or more, and at the corresponding hour next night perhaps only ·4 of a degree apart.

Similarly in the low excretion of uric acid after a course of salicylates, they will be nearer together in the a.m. hours and at 1.30, and I have records of only ·2 to ·4 of a degree of difference at 12.30 or 1.0 p.m. in these circumstances.

We may now consider the action of drugs. So far we see that the hourly, daily, monthly, and yearly excretion of uric acid has to do with variations produced by introduction and the effects of various factors on solubility, while there is no proof that the formation of uric acid relatively to urea alters at all.

Drugs act by increasing or diminishing solubility, and influence excretion accordingly, but there is no evidence that any produce increased formation of uric acid; what has been attributed to this increased formation is probably due either to increased introduction in food, or to increased elimination by solvents.

I found out early that by influencing the solubility of uric acid I could completely vary excretion, and more recently, that by controlling introdnction, I could exercise still more decided control over the amount passing into and through the blood (see fig. 73).

When we recognise the enormous power of uric acid in controlling the circulation it will appear that this knowledge is of the utmost importance in guiding physiology and pathology, and explains facts and sequences otherwise inexplicable.

In speaking of the action of drugs I divide them into (1) those that increase, and (2) those that decrease excretion, and having enumerated those in each class shall indicate the action of each individual drug.

The chief substances increasing the excretion of uric acid are alkalies, colchicum, salicylic acid and its compounds, salicin, salol, aspirin, &c., phosphate of soda, piperazidin, quinine and belladonna.

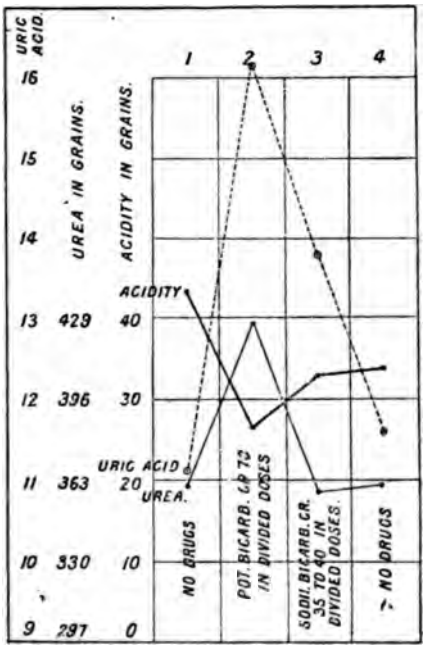

FIG. 6.—PLUS EXCRETION OF URIC ACID PRODUCED BY ALKALIES.

I place alkalies first because they are found in daily action, and have far greater importance than any less common substances. The curves in fig. 6 show the effects of the alkaline salts of potash and soda. They produce a decided fall in the acidity curve in day 2, and keep it more or less low on days 3 and 4. The result is that uric acid which is close to urea on day 1, rises considerably above it on day 2, remains high on day 3, and is still fully half a grain above it on day 4. The rise of urea on day 2 is

not the result of potash but of some alteration in diet or exercise; other things being equal, a fall of acidity and a rise of uric acid tend to depress urea.

Speaking generally and apart from the action of other solvents, it seems the excretion of uric acid from day to day and hour to hour is inversely as the acidity of the urine.

There is evidence that, speaking generally, the fluctuations in the acidity of the urine correspond in direction and extent with fluctuations in the alkalinity of the blood; thus it has been shown by Peiper (*Virchow's Archives*, June, 1899, p. 337) and others, that the alkalinity of the blood is diminished in all fevers save those complicated by dyspnœa and cyanosis, and the acidity of the urine is increased; a good instance being recorded in Sir W. Roberts' work "On Urinary and Renal Diseases," fourth edition (p. 59), where a patient with alkaline urine got erysipelas and the urine became acid during the fever, becoming alkaline again when it subsided (see previous remarks on fig. 5).

Conversely a vegetarian diet diminishes the acidity of the urine and, I believe, increases the alkalinity of the blood. There is, however, one exception to my statement concerning the relation of the excretion of uric acid to the acidity of the urine considered as an index of alkalinity of the blood; and that is where, as in the fits of epilepsy (see cases in chapter vii.), there is a huge excretion of uric acid relatively to urea; for here the acidity of the urine is extremely high and the greater the amount of uric acid present the higher acidity. It thus appears that when a very large amount of uric acid is excreted the acidity of the urine may be no safe index of the alkalinity of the blood, because the acidity of the excretion is to some extent affected by the amount of contained uric acid.

It is generally easy to distinguish this pathological exception for the usual relation between acidity and urea no longer holds good. In the urine excreted after a fit acidity rises but urea is steady or even falls a little (see chapter vii.); the rise of acidity is therefore not due to ordinary urea metabolism, but corresponds with a marked rise in uric acid and may be due to this; the alkalinity of the blood on the other hand varies inversely with the metabolism of urea and is therefore high and rising. A similar rise of acidity, not accompanied by rise of urea, is seen in several of the figures, showing the effects of taking uric acid or xanthin compounds (figs. 25 and 26).

I am indebted to Dr. G. C. Garratt for pointing out that a rise of acidity after a fit of epilepsy is in part due to a rise of the

phosphates excreted in the urine (see also his paper in the *Journal of Physiology*, vol. xxiii., No. 3).

He also shows that phosphates follow closely the acidity curve of the urine, and this is to be expected from the observed relation between the curves of urea and acidity; for the phosphates probably represent the final metabolism of the phosphorus in the albumen molecule just as urea represents the final metabolism of its nitrogen.

There may be larger excretion of phosphates after an epileptic fit as the result of increased metabolism in the tissues of the nerve centres rich in phosphorus,* and this possibly partially accounts for the observed rise of acidity.

If so, part of the increased excretion of uric acid after an epileptic fit is a result not a cause, and there is no exception to my law of solubilities, for phosphates in the blood are solvents of uric acid; but uric acid combining with phosphates diminishes their alkalinity and must thus raise the acidity of the urine.

Sir A. Garrod has shown that the alkalies soda and potash form extremely soluble compounds with uric acid, and phosphate of soda is also well known as a solvent. Fig. 7 shows its effects; here in day 1 uric acid was far below urea owing to the high acidity due to the taking of acids and antipyrin. A drachm of phosphate of soda is taken three times on day 2, and uric acid rises just above urea, which has fallen.

This high urea on day 1 was probably partly due to the low uric acid, because (chapter viii. and elsewhere) everything that brings down uric acid tends to raise urea, or in other words, everything that clears the blood of uric acid quickens metabolism, and stimulates formation and excretion of urea; but as this only lasts a short time urea does not remain high on day 2.

On day 3 a similar dose of phosphate is taken, and uric acid rises more decidedly above urea, and on day 4, when the drug is left off but no other change made, it falls a long way below it.

Phosphate of soda then causes distinctly increased excretion of uric acid, followed by a fall when the drug is stopped; proving, I think, that we are dealing with excretion and not with new formation.

Readers familiar with the treatment of arthritis by alkali will understand that the action of colchicum is simply that of an

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* Zuelzer, "Semiologie des Harns," p. 89 (see also chapter iii.).

alkali, and it decidedly diminishes the acidity of the urine. I must anticipate misunderstanding by saying that this diminished acidity of the urine may not be obvious to those who test it merely with litmus paper, for, as colchicum causes an increased excretion of uric acid it produces, for reasons elsewhere given, a diminished excretion of water, and the urine is more concentrated and may appear even more acid than usual to a litmus test. Nevertheless when we estimate the total excretion of acid for a day we shall find that the administration of colchicum has

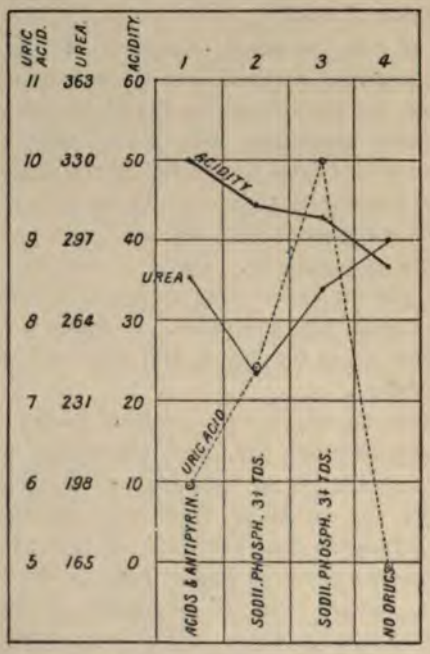

FIG. 7.—PLUS EXCRETION OF URIC ACID PRODUCED BY PHOSPHATE OF SODIUM.

decidedly diminished it. If for instance the total acidity of the day before was equal to say 60 or 70 grains of oxalic acid, it will be found probably that on the first or (better still) the second or third days of the action of colchicum, the total excretion of acid for the day is only equal to 50, 40, or fewer grains of oxalic acid.

If for a moment we grant that colchicum acts simply as

an alkali and dissolves uric acid in the same manner as other alkalies, we shall understand its action, for one of the first effects of colchicum administered in ordinary doses is dyspepsia and increased action of the bowels, and it is not uncommonly given with magnesia and other substances to increase its purgative effect, whilst some authorities have even maintained that colchicum is of little use in gout unless it purges. It is occasionally given with alkaline salts doubtless acting similarly.

Every physiologist who has watched the excretion of urine recognises the fact that all dyspepsia means a fall in its acidity, for practically the main factor is the combustion of albumens, and the more urea produced from albumen the more acid is produced from the non-nitrogenous constituents of the albumen. These two always rise and fall together, so that a rise of urea means a rise of urinary acidity, and a fall in urea a fall in acidity. Now colchicum produces a fall in urea and urinary acidity because all dyspepsia does the same, dyspepsia being accompanied by a diminished digestion and absorption of albumens; and as there is thus less albumen metabolised, the resulting urea and acid products must be considerably diminished. Secondly, colchicum in purging sweeps away more or less considerable quantities of food, with the albuminous constituents unabsorbed. On these facts depends practically the entire activity of colchicum in dissolving uric acid and curing gout, and it is upon an understanding of these that we base our knowledge of the action of colchicum and the advisability of giving it in arthritic cases.

Colchicum acts as an alkali, but has this further effect that when a drachm of citrate of potash is given a fall in the acidity of the urine and a rise in the alkalinity of the blood are produced. But when the citrate of potash is stopped the effects will pass away in the two or three following days. This is not the case with colchicum.

The nett result of the administration of colchicum is more or less dyspepsia and, if administered for some time, more or less subacute catarrh of the whole gastro-intestinal tract, and this will last not only during the administration but for a considerable period afterwards. It weakens and debilitates the patient by gradually lessening the amount of food absorbed, and this weakness will be prolonged because of the unnatural conditions produced in stomach and intestines.

Here is a marked difference between the administration of colchicum and that of an alkali; the effect of the latter is calcu-

lated and determined easily by stopping the dose, the effect of the former is far more intricate and it may not be possible to free the patient from its effects for weeks or even months.

Those conversant with my writings know that I divide the uric acid diseases into two categories, the local or arthritic group and the general or circulation group due to the presence of uric acid in excess in the circulation, where, by partially blocking the capillaries, it interferes with function, nutrition and circulation. Now the result of giving alkali to cure arthritis is to produce in proportion to its success the exactly opposite condition, that of excess of uric acid in the blood (collæmia). Among the more important conditions attendant on collæmia are headache, mental depression, asthma, Bright's disease, diabetes and anæmia, my point being that when we have cured the arthritis by giving solvents (in this case alkali), we can stop the alkali and permit the patient to proceed towards more normal conditions. If however we have cured the arthritis with colchicum it may not be possible to secure these conditions for a considerable time, and meanwhile, supposing the stores of uric acid have been large, the patient is in danger of headache, mental depression, asthma, Bright's disease, diabetes and anæmia, in a word the whole circulation group of uric acid sequences, some of which may prove more serious than the original gout. This has been my experience in not a few cases in which, from anxiety to escape gout, the too lavish or prolonged application of colchicum has produced one of these more fatal troubles, and this observation has always disinclined me to treat arthritis with colchicum, preferring for this and reasons given elsewhere, either salicylates (which are, in proper conditions, by far the best and most powerful solvents of uric acid we have), or failing these, alkalies alone. For these latter though slow as compared with salicylates are fairly certain in their effects, and though less powerful and rapid in action than colchicum are free from the fatal objection that they may set up an uncontrollable sequence in which a patient is driven into a more serious trouble, where, owing to the persistent conditions of dyspepsia and debility set up by the colchicum, we may be unable to intervene.

All collæmia is the first stage of Bright's disease, and the cure or prevention of Bright's disease is the prevention or cure of collæmia. Numbers of people in calling in the too violent action of colchicum for gout have been surprised to find it replaced by more or less intractable Bright's disease.

The explanation is simple; the local group is exchanged for the circulation group, and a painful disease for a dangerous one. If a more manageable solvent is used for gout, there is no reason for this risk.

As to salicylic acid and its compounds, I have shown that they increase excretion of uric acid and that what is known about the compound (salicyluric acid) which they form seems to indicate that it is not only more soluble in water than the salts of uric acid, but also much more so in slightly acid fluids—an important point to which I shall often refer. I should explain with regard to salicyluric acid that it is not a compound of uric and salicylic acids, but of glycocoll (one of the constituents of uric acid) and salicylic acid, just as hippuric acid is a compound of glycocoll and benzoic acid.

What I say with regard to the solubility of salicyluric acid applies to its presence in the blood only, for in the urine it does not give any reaction with Haycraft's process, and is, therefore, so far as my results are concerned, not estimated as uric acid. In so far as a salicylate increases excretion of uric acid, the compound salicyluric acid (possibly formed in the blood) is probably largely reconverted into uric acid and salicylic acid as it passes the kidney (see my experiments with regard to these points in the *Transactions of the Royal Medical and Chirurgical Society*, vol. lxxi., p. 137).

I regret that the statements in standard works of reference on chemistry regarding the solubility of salicyluric acid are not sufficiently definite, so that we must be satisfied with probability.

However, if this somewhat hypothetical chemistry serves meanwhile to remind us of the clinical fact that salicylates are poor solvents of uric acid when the alkalinity of the blood is high and the acidity of the urine low, and that for the same reason it is a mistake to give alkaline salts of sodium or potassium with them (see fig. 71 and cases narrated in chapters ix. and xvi.), it will have served some purpose. (See also uric acid-filter experiments further on.)

Fig. 8 shows the effect of a salicylate on excretion, and I need not describe it at length. It shows a great plus excretion on day 2, the first under the salicylate salt, followed by a fall next day with the same dose; a second rise on days 4 and 5, a fall on day 6, and a great fall on day 7, when the drug was stopped. I have used it for studying the effects of absence of uric acid from the blood, both in physiology and pathology (chapters viii. and xii.).

I think most of the available uric acid was cleared out by the solvent on day 2, hence the fall on day 3, and that the rise on days 4 and 5 was due to some fresh introduction of uric acid with food. This figure unfortunately does not give the water, which would have been low on day 2, followed by more or less diuresis on day 3, for here as elsewhere the water is inversely as the uric acid, which explains the

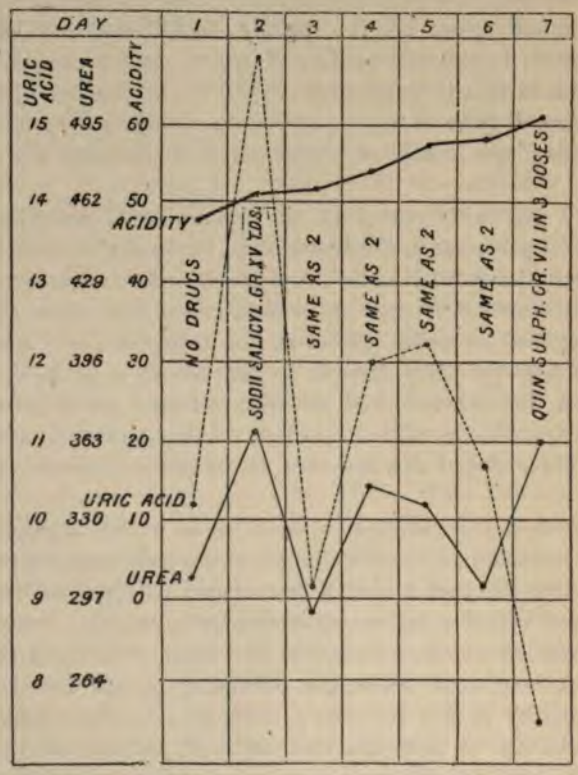

FIG. 8.—PLUS EXCRETION OF URIC ACID PRODUCED BY SALICYLATE OF SODIUM

observation made by others that the diuresis produced by salicylates is absent till the second or third day of their action, this delay depending on the amount of available uric acid, for when this is large uric acid remains high for several days and diuresis will not occur till it falls. This figure, and all the curves of excretion under salicylates show that we are dealing with excretion and not formation of uric acid; if salicylates cause new formation why does

the curve never again attain the height of the first or second day though the drug is continued?

As regards glycocoll or glycocine, its removal from the body is equivalent to the removal of uric acid and, as a matter of experiment, if uric acid and salicylic acid are given together the salicylic aids the elimination of the uric acid and prevents its retention by high acidity (see my experiments in the *Journal of Physiology*, vol. xv., fig. 3). Whether in doing this it first splits the uric acid into glycocoll and urea and later recombines these into uric acid, is a matter of little present importance. The point is that salicylic acid is a solvent and eliminator of uric acid, whether in the body, *e.g.*, in inflamed joints or fibrous tissues, or swallowed in various foods.

I have further shown that with acute rheumatism the salicyl compounds are curative in proportion to their power of eliminating uric acid; that (to take them in order) salicylates are most powerful in both respects, then salol and lastly salicin. I shall point out in chapter xvi. that when the natural solvent action of salicylates is prevented (see previous remarks about salicyluric acid), they raise the temperature and increase the pains of rheumatism, so there is no doubt that these salts cure acute rheumatism just as alkalies (soda and potash) do, by dissolving and eliminating uric acid and that the fever and pain of this disease are entirely due to the irritation of fibrous tissues which uric acid produces.

Phosphate of soda, the ordinary Na_2HPO_4, is a good solvent of uric acid and causes plus excretion, but it can only act in an alkaline medium or while the supply of alkalies is abundant; the presence of any acid, or even the salt of a mineral acid as a sulphate, appears to convert it into the acid phosphate NaH_2PO_4, and the plus excretion of uric acid ceases.

Phosphate of soda should therefore be given with alkalies or when the supply of alkalies in the blood and tissue fluids is good; it will then cause a satisfactory plus excretion of uric acid, as in headache, high tension pulse, and mental depression, when alkalinity is high. Salicylates act best when alkalinity is low, and their action as regards the excretion of uric acid appears to be hindered by the presence of alkali; they are appropriate in fever when alkalinity is generally low, and where there is little or no fever it may be necessary to give them with opium or ammonia which raise the acidity, or in alternate doses with acids to obtain their full effect on the excretion of uric acid. Many failures in the

practical treatment of disease with salicylates are due to ignorance of these facts.

For the same reason aspirin is a powerful solvent of uric acid, being a compound of salicylic and acetic acids without the presence of any alkali. This acid combination aids the solvent power of the salicylic acid so that aspirin will often produce a larger excretion of uric acid than a similar dose of salicylic acid, and will act in conditions of heat and perspiration where salicylate of soda would fail. It may also do well with debility and subnormal temperature where salicylate of soda does little.

I have experimented with piperazidin and it appears to increase

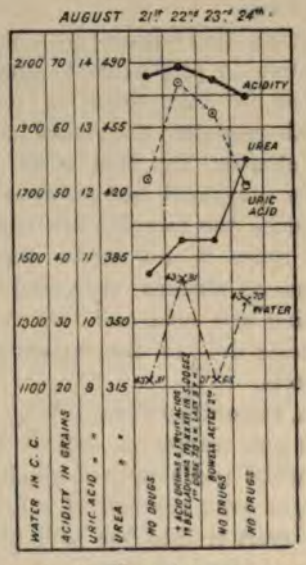

FIG. 9.—PLUS EXCRETION OF URIC ACID PRODUCED BY BELLADONNA.

the excretion of urates, but is certainly not a very powerful excretant and cannot compare with salicylates; unlike salicylates its action is hindered by acids; thus, when the hydrochlorate of piperazidin is taken, the first effect of a dose of 12 to 15 grs. is a minus excretion of urate and diuresis, followed later by some plus excretion which, however, is prolonged.

Belladonna is an interesting drug because its action is the reverse of that of opium.

Opium frees the capillaries, lowers blood pressure, quickens the heart, improves the circulation in the skin, and raises its tempera-

ture (see remarks on fig. 5), increases the urine, and produces mental brilliancy and well-being. Belladonna obstructs the capillaries, raises the blood pressure, slows the heart, slackens the circulation in the skin and lowers its temperature, diminishes the urine, and causes mental dulness and tendency to headache.

I pointed out in the *British Medical Journal* (1889, vol. ii.), in a paper on "The Influence of Opium and Morphine on Uric Acid considered with Reference to their action in Health and Disease," that opium owes the whole of its activity to its action on the solubility and excretion of uric acid, that all its effects are due to its clearing the blood of uric acid owing to its raising acidity, and this again is due to its delaying peristalsis and thus increasing the absorption of nitrogenous and acid substances from the intestines, and especially the large intestine.

We shall see the full interest of this when I point out that belladonna owes its antagonism to opium to its reverse effects on the solubility and excretion of uric acid, these being due to the fact that it increases peristalsis and diminishes the absorption of nitrogen and acid substances from the intestines, thus reversing the action of opium.

Fig. 9 shows the effects of taking ♏ xxxii. of tincture of belladonna (B.P., 1885) in divided doses between the hours of 7 a.m. and 9 p.m. on August 22.

The immediate effect is a decided rise of uric acid, dropping a little on the 23rd, and on the 24th coming below urea.

The effect of belladonna on peristalsis is shown by the fact that the bowels, usually extremely regular, acted twice on the 23rd.

The effect on acidity is not so clear, because on the 22nd, some extraneous force raised the urea, and the dryness of the mouth was so great that acid drinks were taken; on the 23rd and 24th however, there was a decided fall in spite of the fact that urea still rose, and on the 23rd a break in the upward movement of the urea corresponding, no doubt, with the increased action of the bowels.

It will of course be said that belladonna did not diminish the urine, but I suggest that the rise on the 22nd was entirely due, as the figures show,* to the diuresis at night when no doubt the acids produced their full effect and slightly freed the capillaries; in the

* The figures to the left of the water curve represent the hourly excretion of water in sixteen hours of the day, that is, the total excretion of those hours divided by sixteen, similarly the figures to the right of the curve represent the hourly excretion of water in eight hours of the night.

day hours it was not more profuse than on the 21st, in spite of the increased quantity of fluid. And on the 23rd, when acidity had fallen distinctly, and uric acid was still high, the water in the day hours was very scanty.

On several occasions when taking atropine or belladonna, I have had decidedly slow pulse—66 or below that—with all the signs of high blood pressure and threatening of headache.

Belladonna thus ranges itself with the drugs causing an increased excretion of uric acid and many of its physiological effects are common to all.

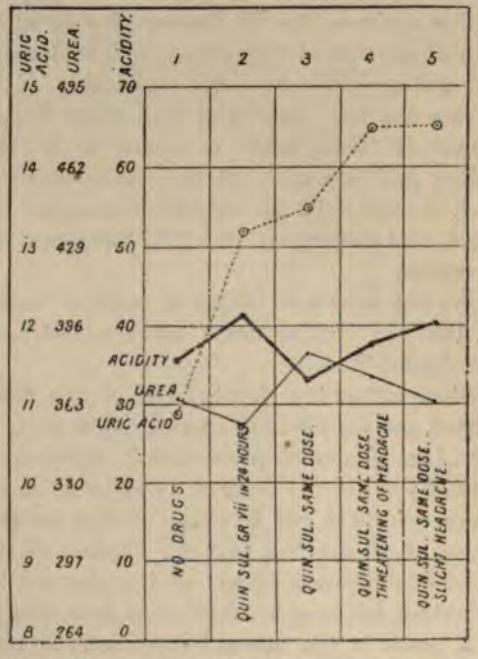

FIG. 10.—PLUS EXCRETION OF URIC ACID PRODUCED BY QUININE.

Quinine increases the excretion of uric acid in the urine, and I am inclined to believe that part of its effect is due to its contracting the spleen, a well-known reservoir of uric acid.

Where the spleen is large, as in malaria, leucocythæmia, &c., and the excretion of uric acid is generally abundant, the exhibition of quinine greatly increases it.

In fig. 10 we see the effects of giving quinine gr. vii. in twenty-four hours; while the drug is continued there is a fairly steady

rise in the excretion of uric acid which seems independent of the fluctuations of acidity.

When first observing the increase of uric acid under quinine I believed it to be a plus formation of uric acid which I had not otherwise met with and therefore regarded with interest; but when I gave a course of salicylate before the quinine (*i.e.*, removed all the available uric acid from the spleen) it no longer caused so large an excretion, and I concluded I had to do chiefly with excretion and not with formation, both in normal conditions and where the spleen is enlarged (see the last day of fig. 8).

When quinine squeezes the uric acid, as we are supposing, out of the spleen, it causes more or less collæmia, and the signs of this are among the prominent symptoms of quinism. The quinine headache is well known. It is said to do harm in epilepsy or may even produce it; it is also recorded that quinine given in large doses for malaria may produce hæmoglobinuria (*Progrès Médicale*, July, 1888, p. 4), and for my arguments about this latter see chapter xii.

I have met patients with large spleens who objected to quinine as causing headache, and this I should expect (see also *Brain*, Spring number, 1891, p. 73). Sir T. Lauder Brunton, in a most favourable mention of my work ("Cavendish Lecture," 1891, *Lancet*, vol. i., 1891, p. 1361), says it enabled him to understand how a patient with a very large spleen was able to continue passing uratic gravel. Sir T. Lauder Brunton had almost concluded that there must be a stone in his bladder of which portions were being excreted, but after death no stone was found. No doubt he was passing a great excess of urate, having a relation to urea of 1—10 or 1—12, and some of this would, from time to time, from absence of pigment or salts or excess of acids, &c. (see the late Sir W. Roberts, *Medico-Chirurgical Transactions*, vol. lxxiii., p. 266) be deposited in the urinary passages, so that our knowledge of the formation and excretion of urates is likely to throw some light on the formation of calculi (see also *Lancet*, February, 1888, p. 1010, for a case in which there was a large spleen, and a urate calculus quickly formed).

Ranke and others state that quinine diminishes the uric acid in the urine, and this statement as diametrically opposed to my own results puzzled me, but I believe it can be easily explained.

Sulphate of quinine has a double action on uric acid, that is to say, it has the action of a sulphate which, as I shall show presently, causes retention of uric acid and clears the blood, and it also acts on the spleen, causing collæmia and a plus excretion of uric acid.

If a small dose (6 grs. in twenty-four hours) is taken, and its

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effects hourly watched there are first, a rise of acidity of urine, minus excretion of uric acid, freeing of capillaries and plus excretion of water (diuresis); later, acidity falls and collæmia sets in; with this there is slower pulse, diminishing urinary water, and a tendency to headache, and generally with small doses the second stage of collæmia and plus excretion outweighs the minus excretion of the first stage. With large doses of sulphate—6 to 15 grs. (and Ranke and others specially mention large doses)—the effect would be more powerful and lasting, and the minus excretion

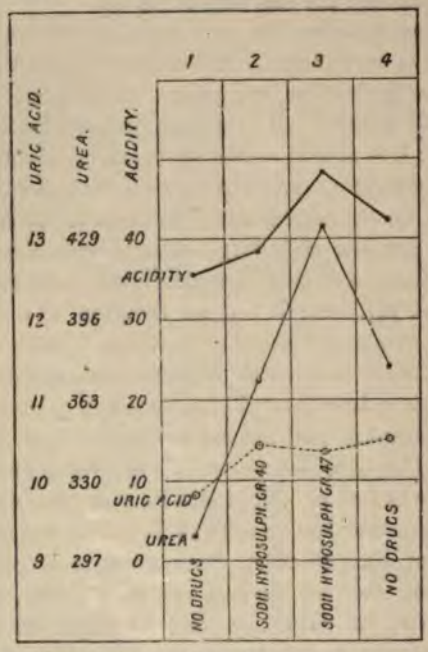

FIG. 11.—RETENTION OF URIC ACID PRODUCED BY ACIDS.

of uric acid, with reduced arterial tension and diuresis, might continue twenty-four hours or more; hence the difference between my results and those of others is due to difference of dose, and apparent rather than real.

Quinine is an alkaloid or xanthin, and a certain proportion of the quantity swallowed is equivalent to uric acid. If we take the chemical formula for acid sulphate of quinine and remove the elements of uric acid, these bear a proportion to the entire acid sulphate of about 1 to 5, and several experiments made by taking known quantities of the sulphate and watching the corresponding

increase in the excretion of uric acid at a time when there was no introduction and, as far as possible, no other uric acid available for solution gave results close to this theoretical calculation.

Whether the xanthin element in quinine will account for the whole increased excretion in fig. 10 is another matter; but there is little room for doubt that where quinine is given in large doses as for malaria, much of the following excretion of uric acid may be due to this introduction. Other vegetable alkaloids such as strychnia seem to give similar results, and increase the excretion of uric acid in proportion to their xanthin elements.

There is an interesting note at the end of "Boerhaave's Aphorisms," London, 1742; and I am indebted to Mr. Justice Garrison, M.D., Merchantville, New Jersey, formerly a member of the profession, for a reference to the section on Rheumatism, viz., 1282 to 1288, as follows:—

"N.B.—Our author (Boerhaave) had forgot to treat of this disease in his former editions (*i.e.*, prior to 1728), and truly I never heard him make any mention of it in his lectures during two years I constantly attended him; nor does it seem to be a disease much known, or at least distinguished by any particular name in Holland or most places beyond the sea, and consequently seems to be more peculiar to this Isle. Consult, therefore, about its differences and proper cure the never-to-be-forgotten Doctors Sydenham and Musgrove. The first distinguishes rightly between the inflammatory and scorbutic rheumatism; and for the latter he advises an excellent electuary and apozem to be continued for some time. He mentions that it chiefly invades women who have had occasion to take large quantities of *Jesuit's Bark*,* owning, however, at the same time that this is the sole mischief which he knew was done by that medicine."

I was interested in this as in the spring of 1904, I was given some tinct. cinchonæ co., for an attack of diphtheria, and it quickly produced lumbago followed later by a headache, giving visible and tangible signs of the introduction of uric acid into a body otherwise fairly free of it.

It is worth noting that rheumatism, prior to 1728, was better known in England than in Holland. Had our ancestors even then begun to feed more unwisely than their neighbours?

The chief substances which diminish the excretion of uric acid are acids, iron, lead, mercury, silver, copper, zinc, manganese, and other metals, lithia, calcium chloride, and other salts of calcium,

* Old name for cinchona.

acid phosphate of soda, some sulphates, chlorides, &c., and many substances which directly or indirectly raise the acidity, or otherwise form insoluble compounds with uric acid, as opium, cocaine, the iodides, antipyrin, ammonium salts, the nitrites, some hyposulphites and other compounds of sulphur, and many less well known substances.

All these diminish excretion, and cause retention and accumulation. They clear it from the blood and produce the symptoms of its absence from the circulation, which are chiefly the reverse of those produced by its presence. They drive the urates from the circulation into the joints and fibrous tissues (where their arrival may be evidenced by pricking and shooting pains, see gout), also into the liver, spleen, and other organs.

I place acids at the head of the list because their action dominates the physiology of daily life, and their range is infinitely more extensive than that of the others whose presence is accidental and temporary. Fig. 11 shows us the effects of the rise of acidity produced by taking hyposulphite of sodium. Acidity rises moderately on day 2, more decidedly on day 3, and falls again on day 4, after the drug is stopped. Uric acid, which is above urea on day 1, falls below on day 2, a long way below on day 3, and is but a comparatively small distance below on day 4, as acidity falls again.

Acidity of urine bears a fairly constant relation to urea, both tending to rise and fall together, and that I have given, 1 of acidity (reckoned as oxalic acid) to 6·8 of urea, is very constant. Whatever (food, exercise, &c.) raises urea raises acidity, and *vice versâ;* thus a meal of mutton or beef will increase urea, and it has been suggested that the concomitant rise in acidity is due to the salts contained in the meat (Senator *Ziemssen*, vol. xvi. pp. 126-7). We must remember also that the albumen molecule contains not only nitrogen but sulphur and phosphorus, and that the metabolism which converts nitrogen into urea will also probably convert sulphur and phosphorus into acid substances, hence the very close relation just mentioned between excretion of urea and of acid substances in the urine. Their general relation is that the rise of acidity follows some hours after the rise of urea, and it appears as if the metabolism of phosphorus and sulphur is slower than that of nitrogen. Thus meat not only increases the formation of urate but promotes retention and also introduces urate ready formed. Acids occur in many articles of diet, especially in wines, beers, and other drinks, cider, lemonade, &c. Sir A. Garrod attributed the

gout-producing power of beers and certain wines to some unfermented matters, but I have shown (*British Medical Journal*, vol. ii., 1888, p. 10, 11), that the acids which they all contain in large quantity and without which beers, for instance, would neither keep nor be palatable, sufficiently account for their gout-producing powers. Acids, again, may be formed by certain fermentation processes in digestion, a question which M. Bouchard has very ably worked out (*Leçons sur les Auto-Intoxications*, p. 172).

Sir A. Garrod has shown (prev. ref., p. 258) that suppression of perspiration is immediately followed by a rise in acidity of the urine and I can prove that increase of perspiration diminishes this acidity (see also fig. 72). Hence we can explain how hot rooms or warm south-west winds diminish acidity, increase excretion of uric acid, and produce the feeling of languor and depression due to its presence in the circulation; also how a cold north-east wind raises acidity and produces the reverse effect, making us cheerful and brisk.*

Last, but not least, deficient oxidation lowers acidity. According to Peiper, fevers accompanied by dyspnœa and cyanosis form exceptions to the rule that fever raises the acidity of the urine and diminishes the alkalinity of the blood, and it seems to me that deficient oxidation must mean deficient formation of acids (See *St. Bartholomew's Hospital Reports*, vol. xxvi., p. 19. of my paper), hence the cause of the above exception.

We shall see that fevers accompanied by dyspnœa and cyanosis are also exceptions in that capillary reflux is slow and blood pressure high, *i.e.*, the blood is full of uric acid instead of free or nearly free from it.

I have little doubt that many of the headaches caused by theatres, church and other meetings are due to heat and deficiency of oxygen, both of which lower the acidity of the urine, increase the alkalinity of the blood, and flood it with any uric acid ready for solution. But if none is available none of these conditions result, and a knowledge of these simple facts enables me to explain hundreds of sequences in the physiology and pathology of everyday life.

With regard to iron and lead, Sir A. Garrod shows that these substances form insoluble urates, and they therefore fall within my rule and diminish excretion of uric acid because the compounds they form with it are insoluble, just as alkalies (potash and soda),

* As to the fact that sweat at the time of its discharge from the ducts is normally acid, see Heuss, "*Monatschr. fur. prakt. Derm.*," No. 9, 1892.

phosphates and salicylates increase excretion because they form soluble compounds.

The first effects, then, of iron and lead are to diminish excretion of uric acid and clear it out of the blood, and at this stage they produce the symptoms due to its absence and may involve the pricking and shooting pains indicating its presence in joints and fibrous tissues.

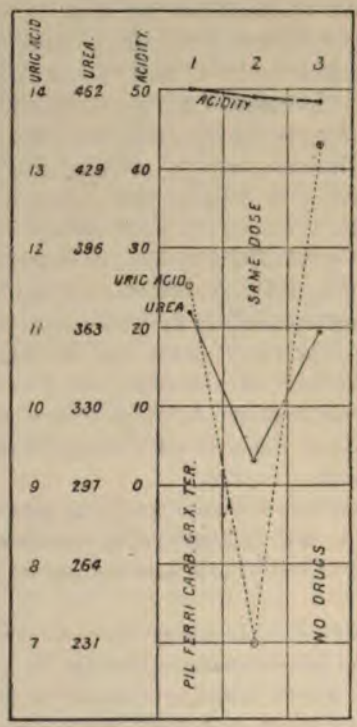

FIG. 12.—RETENTION OF URIC ACID PRODUCED BY IRON.

Fig. 12 shows the effect of giving gr. x. of pil. ferri carb. three times a day. There is a marked fall of uric acid on the second day, followed by a rise—which I call a rebound—on the third day when no iron is taken. This large excretion on day 3 is the result of increasing solubility of the blood, now containing less iron, and also of diminished excretion or retention of uric acid on day 2; just as occurs in the physiological excretion of the alkaline tide of the morning hours. See remarks on figs. 1, 2 and 3.

Fig. 13 shows the effect of giving 1 gr. of acetate of lead three times a day for two days. Here the fall of uric acid occurs immediately, and there is no rise of acidity to account for it, therefore it is the result of the insoluble compound uric acid forms with lead.

This does not last; in spite of the lead being continued, uric acid is above urea next day. Acidity, however, falls decidedly and causes the rise of uric acid. This figure therefore proves that no drug causing intestinal irritation continues to cause diminished excretion of uric acid, no matter how insoluble

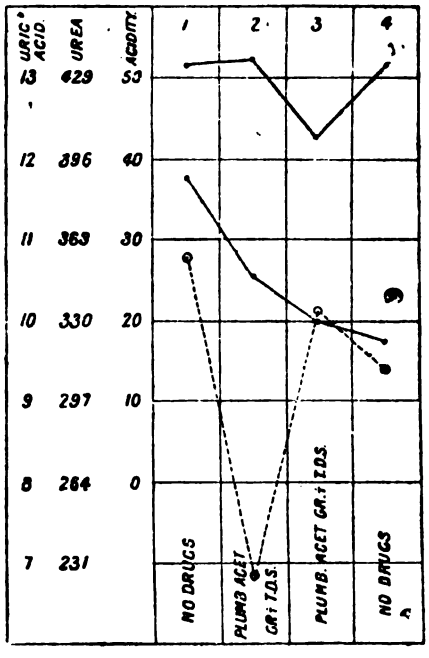

FIG. 13.—RETENTION OF URIC ACID PRODUCED BY LEAD.

may be the compound formed. For intestinal irritation causes a fall of urea and acidity, and uric acid passes into solution with the neutral phosphates of the blood and disregards (so to speak) the lead. Exactly the same thing occurs with mercury, copper, zinc, silver, or any other metal whose urate is insoluble, and the moment they cause intestinal irritation, or purgation, they cease to lower the excretion of uric acid. This fact is of enormous importance for correct understanding of the physiology and pathology of uric acid, because it shows that every-

thing, food, drink, drug, or disease product, that causes gastro-intestinal irritation will produce a fall of urea and acidity of the urine and a plus excretion of uric acid; in other words, it will flood the blood with uric acid, and the results of this collæmia will be promptly felt.

We have seen that increase of peristalsis is the cause of collæmia and of many effects which belladonna produces (fig. 9). We shall see that the diminished peristalsis of opium or morphine is the cause of their action in clearing the blood of uric acid, and so of many of their important effects; and we shall meet with results of intestinal irritation in nearly all these diseases due to uric acid (especially such as headache, epilepsy, mental depression, hæmoglobinuria, anæmia, and Bright's disease, which are due to excess of uric acid in the blood); in these and many others, dyspepsia and its effects in producing collæmia are most deadly.

But to return to fig. 13: on day 3 the lead produced intestinal pain and griping, diminished appetite, deficient digestion and absorption followed, hence a fall of urea and acidity, and though the lead in the blood no doubt combined with some uric acid the rising alkalinity dissolved a considerable quantity of that retained on day 2, and no retention followed on day 3.

In this way iron or lead will produce or precipitate the arthritis of gout or rheumatism, but relieve headache or mental depression due to uric acid in the blood.

This is the first stage of their action and it is necessary to remember the rebound, or confusion as to cause and effect will result.

Take lead again, as the history of plumbism is well known; its first effect is to store in the liver, spleen,* joints, and other fibrous tissues some 3—4 or more grains of uric acid; it then promotes intestinal irritation (possibly from a deposition of insoluble urate of lead in the fibrous tissues of the intestinal walls); this causes pain, nausea, and distaste for food, and quickly brings about a fall in urea and acidity, when the rising alkalinity of the blood dissolves part of the 3 or 4 grs. retained and floods the blood with uric acid. Hence with lead colic we have headache, depression, slow high tension pulse, and perhaps even epilepsy—all due, as I shall show, to the excess of uric acid in circulation. Anyone who experiments with lead can produce not only the fluctuations in uric acid (first

* See "Lead Poisoning," by Professor T. Oliver, p. 102, *et seq.*; Young J. Pentland, 1891.

retention, and then plus excretion), but also the signs and symptoms of its presence or absence from the blood in the sequence I have mentioned, and any clinical observer will support my statement that these are the main symptoms of acute and chronic plumbism, which can thus not only be explained but imitated at pleasure, either with lead or other members of the group, such as opium, cocaine, mercury or other metals or acids.

To such an extent is this the case, that I believe many cases of intestinal colic are due to urate irritation, of which urate of lead forms a single instance, and in corroboration I may mention that salicylate of soda is a valuable remedy in all these forms of colic—a discovery which I made accidentally (see chap. x.).

The similar rebound after iron accounts for the well known relapse of chlorosis or anæmia treated by it. The iron is taken for a long time, and in clearing the blood of uric acid stimulates nutrition and metabolism to an upward movement continuing weeks or months after the metal has been stopped. But as iron relieves chlorosis by clearing the blood of uric acid, and not by elimination but by retention in the tissues, when the iron is gone and the stimulation of nutrition has yielded to time or some definite cause of depression (such as overwork), the chlorosis will relapse and be worse. When, however, it is treated by a diet which clears the body of uric acid and keeps it clear, the improvement of the blood is continuous.

I must allude to lithia because it is an apparent exception—one however, which proves my rule.

Fig. 14 shows the effect of taking citrate of lithia, and I am glad to see that my results have been corroborated by the researches of Professor Oliver (see prev. ref., p. 107). On day 1 uric acid is nearly two grains below its ordinary relation to urea, and on day 2 it falls still further; on day 3 without lithia, it rises a little, and on day 4 still more decidedly, getting above urea. Yet on day 2 we should have expected uric acid to rise with the fall of acidity, and it rose on days 3 and 4 in spite of a rise of acidity.

A fall of acidity similar to that on day 2 is, I believe, a constant result of taking lithia, but the fall is never accompanied by a rise in excretion of uric acid.

I believe the ordinary effect of a fall in acidity of the urine and a rise in alkalinity of the blood, is that the phosphates of the blood increase their solvent power, and that when the acidity of the urine rises and the alkalinity of the blood falls, this diminishes; there is here obviously some cause preventing the phosphates in the blood from dissolving the uric acid.

Sir A. Garrod has shown that urate of lithia is one of the most soluble of all urates, and yet lithia diminishes the excretion of uric acid.

If I had been unable to explain this fact I should have given up my quest, and regarded uric acid as an insoluble enigma, but fortunately the difficulty had been solved for me. In a reference (which I owe to Dr. Neale's Digest) to the *Lancet*, 1860, vol. ii., p. 185, I found it had been pointed out in a work on chemistry by Rose ("Chemical Analysis," p. 15), that lithia

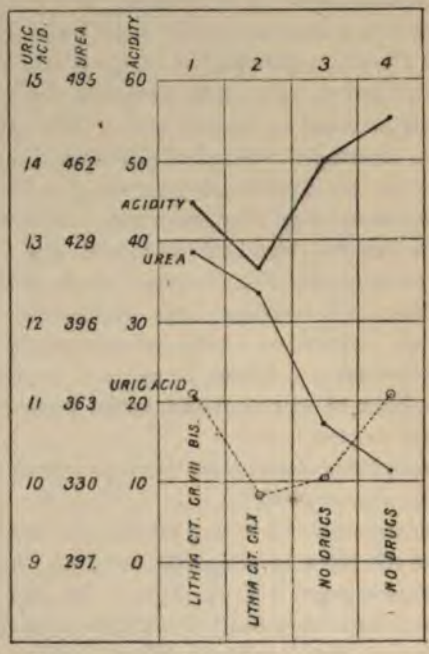

FIG. 14.—RETENTION OF URIC ACID PRODUCED BY LITHIA.

given by the mouth was no use as a solvent of uric acid, because it "forms a nearly insoluble triple phosphate with phosphate of soda, or with the triple phosphate of ammonia and soda, salts generally present in animal fluids."

Here was a simple explanation. The lithia did not cause a plus excretion of uric acid because it never reached it, being waylaid by the phosphates and triple phosphates; this would explain its not causing a plus excretion of uric acid, but why the minus excretion or retention? The answer is simple, and was suggested to me by Mr. J. E. Saul, F.I.C. I have mentioned before that phosphate

of soda is a good solvent of uric acid, and, with an alkali, increases its excretion; now phosphate of soda is a normal constituent of the blood and is generally there in presence of an alkali, *i.e.*, in a condition to act as a solvent of uric acid, so that the lithia in forming an insoluble compound (well known to chemists) with the above phosphates, removes from the blood one of the natural solvents and we see not only why lithia causes no plus excretion of uric acid, but why it causes retention. There is here no exception to my law of solubilities.

In the test tube lithia is a solvent of uric acid, but in the body its chemical combinations with phosphates not only prevent its action but also segregate a certain amount of phosphate.

Lithia relieves arthritis by clearing the blood of uric acid; not, as was supposed, by elimination but by retention, and in the chapters dealing with arthritis we shall see that sulphates, chlorides, iodides, acids, and other remedies act similarly. Many people have questioned me about the action of lithia and its several compounds; so far as I know they all diminish excretion of uric acid and retain it. They are therefore useful in the circulation group of uric acid diseases (as headache, depression, asthma, anæmia, Bright's disease) in clearing the blood of poison, and possibly under certain conditions may relieve arthritis, acting as do several drugs mentioned in the previous paragraph. On the other hand, lithia and its compounds may, in curing the circulatory group, like other retentive drugs, produce arthritis, lumbago and other troubles by driving uric acid into the tissues. The point about lithia is, that it does produce retention, and not, as was thought, elimination; and its effect on circulation, blood granules, or urinary water will certify this fact. Any compound of lithia producing diuresis is causing at the same time retention of uric acid, for urinary water is inversely as uric acid.

At the suggestion of Sir Dyce Duckworth (see "A Treatise on Gout," p. 373), I investigated the action of manganese on the excretion of urates, finding that it produced retention and pains in the joints; therefore, and probably for the same reason it acts like calcium, iron, lead, mercury, and other metals, forming insoluble compounds with uric acid.

Urate of calcium is very insoluble,* and chloride of calcium has an acid reaction, hence it probably doubly diminishes excretion

* One in 2,800 parts of water; Sir A. Garrod's Lectures, *British Medical Journal*, January, 1883, p. 495.

of uric acid. When administered internally it generally produces, to a marked extent, a condition of happiness, well-being, and good temper, and this is a sign of absence of uric acid from the blood.

Dr. G. Thin (*British Medical Journal*, vol. ii., 1891, p. 91) opines that the consumption of water containing lime develops gouty conditions; doubtless it acts in the same way as lead contamination of water; but if people reduced their tea, pulses and animal food, and thus their introduction of uric acid, neither lime, lead, nor acids would harm them materially.

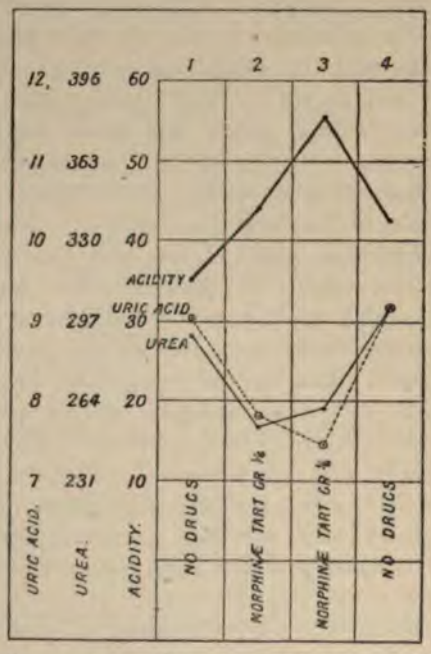

FIG. 15.—RETENTION OF URIC ACID PRODUCED BY MORPHINE.

Acid phosphate of soda, or ordinary phosphate of soda given with a little phosphoric acid or in conditions of high acidity, causes retention rather than plus excretion of uric acid.

So also the salts of the mineral acids, sulphates, chlorides, &c., raise the acidity of the urine and produce a minus excretion or retention; possibly to some extent, by changing the phosphates of the blood into acid phosphates when they cannot act as solvents of uric acid. I have shown that while neutral phos-

phate of soda is a good solvent and produces a plus excretion of uric acid, it cannot act thus if a small quantity of sulphate of soda is given with it (*Medico-Chirurgical Transactions*, vol. lxxii., p. 402).

Of opium I have elsewhere spoken, and fig. 15 shows the effect of taking two small doses, gr. $\frac{1}{6}$ of tartrate of morphine, the first at 11 p.m. on day 2, and the second at 8 a.m. on day 3. The dose on day 2 was too late to produce much effect, as the large daily excretion of uric acid was over before 11 p.m.; it did, however, produce some rise of acidity. That on day 3 was taken early in the morning and caused an increased rise of acidity, though urea rose little and uric acid on this day falls below urea. Probably the chief rise of acidity caused by this second dose was absent till some 4 or 5 hours after it was swallowed, and by this time the alkaline tide was nearly over (see figs. 2 and 3), and the effect on the excretion of uric acid was not great. The dose was very small, and as only one was taken there was time for both retention and rebound in the same twenty-four hours, so that the effect would have shown better in hourly curves. It is certain that opium and morphine raise the acidity of the urine, and diminish the excretion of uric acid and that many of their physiological effects are due to this. Morphine has long been used as a remedy in the uric acid headache.

As with other members of this group the first action of opium is followed by a rebound in which the blood is flooded with uric acid, and the signs of its excess are seen in headache, depression, and general misery, with slow high tension pulse, accompanying the second stage of opium action (see fig. 35). These are the symptoms, driving the victim of the morphine habit to obtain once more the first-stage action and temporary relief. In accordance with this reasoning, if salicylate of soda is given with or in sequence to the first dose of opium it prevents retention of uric acid, and the opium rebound on the following day is absent or greatly modified.

I suggest therefore (*British Medical Journal*, previous reference) the use of salicylates in throwing off the morphine habit, and I know many cases where this course has succeeded.

A medical man who had been taking morphine since a severe and dangerous illness wrote to me for advice, and I suggested, among other things, a plan of using the salicylates.

I have since heard that this was successful, and that he had discontinued the morphine with comparative ease and without insomnia. He added, "I shall always remember you with grati-

tude as having shown me the way to give up the habit, and I am sure that without the salicylates I should only have been able to do so with the greatest difficulty."

For myself a dose or two of salicylates after opium completely prevents the opium rebound, and no high blood pressure, headache, depression, or other ill effect from the drug follows, but I have only tried it after small doses of opium and morphine not continued for more than a day or two.

I hear from Mr. Hope-Lewis, of Auckland, New Zealand, that in

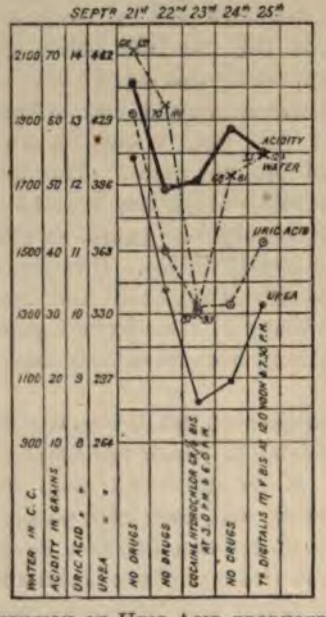

FIG. 16.—RETENTION OF URIC ACID PRODUCED BY COCAINE.

the case of a patient who took morphine, suffering in consequence from intense irritation of skin and formication, 20-gr. doses of salicylate every four hours gave prompt relief, and this would be worth trying in cases where the medicinal use of morphine causes irritation of the skin (see chap. xi.).

Captain W. G. Beyts, R.A.M.C., tells me that he finds salicylate completely successful in the morphine habit in India, and very useful in preventing the after-effects of single doses of morphine, which he no longer dreads giving.

The combination of opium and salicylate is extremely useful in

the practical treatment of disease, for opium produces a condition (high and rising acidity) favourable to the best action of salicylates, and salicylates prevent the after-effects of the opium, and diminish or remove the risk of an opium crave.

The action of cocaine, so far as uric acid is concerned, resembles that of morphine; it produces happiness and well-being, followed by a second stage of misery and depression, and is taken in excess for the same reasons and with even more deadly effect (see *British Medical Journal*, 1902, vol. i., p. 1020).

Fig. 16 shows the effect of two doses of gr. $\frac{1}{8}$ of hydrochlorate of cocaine taken at 3 and at 6 p.m. on September 23.

On September 22 there was a great fall of urea and acidity, and the fall of urea was continued on the 23rd.

As a result there was in the alkaline tide of the 23rd, as shown by the scanty urine, only 37 cc. per hour, a decided plus excretion of uric acid and some excess in the blood; and this collæmia causing uncomfortable symptoms, I took the cocaine.

As with morphine in the last figure, the effect would have shown better in hour to hour curves. The cocaine came too late to affect the previous large excretion of uric acid, hence uric acid exceeds its normal relation to urea by nearly one and a half grains; I have no doubt that but for the cocaine it would have been higher.

The effect on acidity was marked, for on the 23rd, in spite of the further large fall of urea, it rose slightly; on the 24th it rose decidedly, and on the 25th fell, in spite of a rise of urea, showing that the cause of its rise on the 23rd and 24th was removed. On the evening of the 23rd, the cocaine produced marked well-being with free capillaries and absence of mental depression and fatigue (see the similar effects of mercury in fig. 48), and though the urine of the night hours was not so high as during the previous night, it was two and a half times as much as that of the day, indicating that the capillaries were obstructed during the day and free during the night (see remarks on excretion of water in fig. 3).

The effect of the cocaine prevented the continued fall of acidity on the 23rd, and raised it decidedly on the 24th, and therefore uric acid was not nearly so high on the 23rd and 24th as seemed probable, owing to the great fall of urea on the 22nd and 23rd.

In my own case cocaine so soon produces intestinal colic that I have been unable to repeat these experiments as often as I desired, but it assuredly affects uric acid in the same way as morphine and produces identical feelings of well-being—indeed, each one of the retentive drugs does so to a more or less marked extent.

The action on acidity in this figure is clear, and there cannot be much doubt that the physiological effects of cocaine are due to this and to its effects on the solubility of uric acid. Cocaine causes slight constipation and probably raises the acidity in the same way as morphine, by causing coprostasis.

Cocaine, like morphine, produces low tension and quick pulse owing to freed capillaries, and hence improved and quickened circulation in the brain, with mental brilliancy and well-being, and relaxation of the vessels in the kidney, with a marked diuresis of a pale and watery urine.

Later comes the rebound. The uric acid cleared out of the blood by the first action is got into solution, the capillaries are obstructed, and tension high, hence urine is scanty and of high specific gravity, and there are lethargy and depression, with sleepiness (as with all high blood pressure). Repetition of the dose to secure the relief of its first action is sought and chronic cocainism begun.

I believe cocaine, like morphine, owes much of its effect to its action on uric acid, and that salicylate of soda may be as useful in cocainism as in morphinism. For interesting facts about the action of cocaine, see Dr. A. Fullerton, *Lancet*, February, 1891, p. 663.

In the action of these drugs we have the best illustration of what I have said in "Diet and Food" (ed. 6, p. 119, *et seq.*) that all stimulation is wrong. It calls out reserves and if frequently repeated leads to physiological bankruptcy, the condition of the morphine or cocaine *habitué*.

CHAPTER III.

Formation and Excretion of Uric Acid (*continued*).

Mercury is an interesting drug causing retention of urates. I have written about it elsewhere (see *British Medical Journal*, vol. i., 1890, p. 1241).

Fig. 17 shows very well its action on uric acid, which on day 1 is a little below urea; on day 2, as the effect of half a grain of calomel it is far below urea, and on day 3, when no drugs are given, it bears about the same relation to urea as it did on day 1. Note the marked diuresis on day 2, corresponding with the greatest retention of urate, its clearance from the blood, and the resultant free capillary circulation (see chapter v.).

Mercury sometimes, like cocaine, lead, &c., causes considerable intestinal pain and colic.

I suggest that low blood pressure and diuresis (known results of the action of mercury) are due to its effects on uric acid, for other drugs having similar effects produce similar symptoms.

Speaking of mercury, Sir A. Garrod does not, so far as I know, allude to the solubility of its urates, nor is this mentioned in his table of solubilities of urates (*British Medical Journal*, vol. i., 1883, p. 495).

Yet it appears probable that mercury causes retention of uric acid, and clears it from the blood for the same reason as iron and lead, because their urates are insoluble. Mr. J. E. Saul, F.I.C., kindly furnishes this statement on the subject:—

"I find that a solution of neutral lithium urate, treated with solution of mercuric chloride, yields a curdy white precipitate practically insoluble in cold water. On boiling, slight decomposition occurs, the precipitate becoming yellowish — possibly owing to the formation of an oxysalt. On treating the first-mentioned precipitate with acetic acid, or a trace of hydrochloric acid, solution, slowly in the former case and immediately in the latter, takes place. Borax

or alkalies exercise no solvent action. These experiments show that neutral mercuric urate is insoluble, but that the salt will dissolve in the presence of acid though doubtless with decomposition.

"I have also examined the behaviour of neutral alkali urate with solution of mercurious nitrate. I find that a yellowish precipitate insoluble in water, is immediately produced; the precipitate rapidly darkening in colour, and ultimately becoming grey-black from reduc-

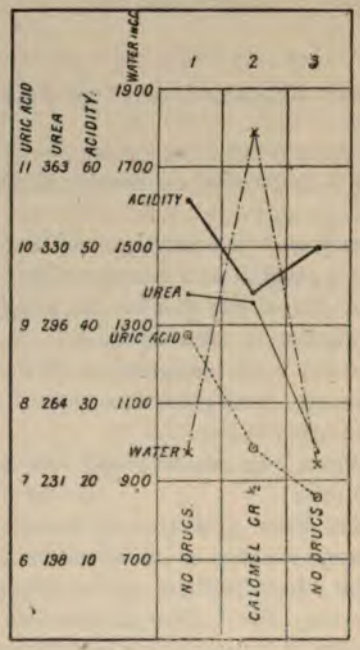

FIG. 17.—RETENTION OF URIC ACID PRODUCED BY MERCURY.

Note that on day 2 uric acid falls in spite of a marked fall in acidity, which apart from the action of mercury, would have made it rise.

tion. In the presence of nitric acid no precipitate is obtained; but if acetic acid be substituted, a partial precipitation slowly takes place.

(*Signed*) "J. E. SAUL."

Thus there is reason to believe that the urates of mercury are insoluble in water, neutral solutions, alkalies, or in solution of borax, and the blood being practically an alkaline solution they are probably insoluble in the blood.

Mercury, therefore, lessens excretion of uric acid in the urine, clears it from the blood, and retains it in the body, because together they form an insoluble compound, and it thus conforms to my law of solubilities. The well-known action of mercury on pulse-rate and blood pressure and the flow of urine, are also instances of the laws I have formulated on their correlation with uric acid. Some object that the uric acid retained by the mercury is much more than could combine with it as an urate; but, as I shall point out in chapter iv., the mercury, if it clears the

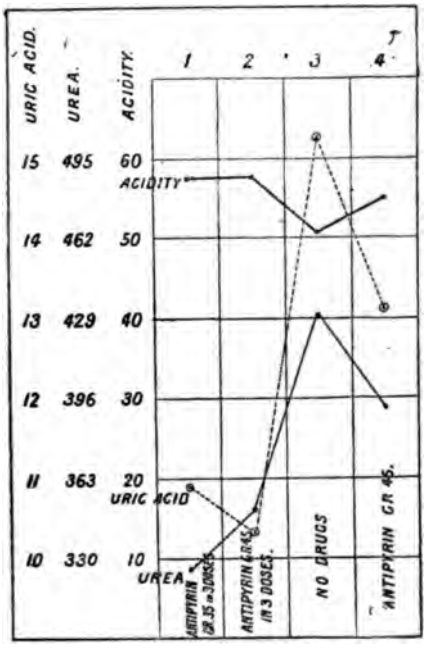

FIG. 18.—RETENTION OF URIC ACID PRODUCED BY ANTIPYRIN.

blood of uric acid for even one or two hours, starts an upward metabolism with a rise of urea and urinary acidity and a fall in alkalinity of the blood, and this latter causes further retention of uric acid which may continue for six or eight hours more. This effect is better seen in hourly than in day curves, as in fig. 17, but is also visible to some extent in fig. 48.

It is extremely probable that the urates of other metals such as zinc and silver, are also insoluble, and indeed Haycraft's process for the estimation of uric acid depends upon the insolubility of the

urate of silver. I believe the so-called tonic action of these drugs, of iron and manganese, and of acids, is due to their clearing the blood of uric acid, and thus improving circulation in the brain and other portions of the nervous system. It is interesting to remember that zinc, like mercury and lead, may produce colic (Ringer, " Handbook of Therapeutics," ed. xii., p. 254).

I suggest that antipyrin cures headache by acting as an acid, and its administration is always followed by increased acidity of the urine.

Fig. 18 shows the effects of antipyrin on this acidity which on days 1 and 2 rises and remains high, on day 2 uric acid falls below urea (probably the antipyrin came too late to affect the alkaline tide of day 1, and the greater part of the urate excretion had already taken place). On day 3 no drug was taken and acidity fell decidedly though urea rose and in normal conditions acidity would have risen also; the antipyrin had, however, raised it so much on the previous days that the moment the drug was withdrawn it fell. On day 4 antipyrin was again given, acidity rose in spite of falling urea, and uric acid was lowered nearer to urea.

We see how antipyrin cures a uric acid headache. It raises acidity and clears the blood of uric acid, producing all the concomitant symptoms of mental content, low tension, quick pulse, joint pains and diuresis. It acts as an acid and I myself prefer to give an acid.

Strychnine causes marked rise in urinary acidity and cures headache. I believe this is because it improves stomachic conditions and promotes digestion and absorption of food, which in headache with nausea are often at a standstill; probably it does this by improving muscle and heart powers and so aiding circulation. Like its congeners it often causes pricking and shooting pains in the joints.

Hyposulphite of soda produces a very marked rise in acidity of the urine, possibly by formation of sulphurous acid or the further oxidation of sulphur, and it reproduces the effects of the administration of a strong dose of acid (see fig. 11).

I consider it probable that nitrites act similarly, and by the formation of nitrous acid diminish the alkalinity of the blood and raise the acidity of the urine, which they certainly do (see figs. 19 and 20).

This granted, the well-known effects of nitrites on the pulse rate and tension may be explained by their acting as acids on the solubility of uric acid.

In favour of this hypothesis is the fact that an acid injected into a vein affects the pulse as a nitrite. I observe that nitro-glycerine taken by the mouth does not exert its maximum effect on blood pressure for some seven or eight minutes, and with a volatile substance rapidly diffused through the body this is a considerable time. With uric acid I conclude the action of an acid or substance interfering with its solubility is as rapid as that of precipitation in a test tube, and practically instantaneous. I do not suppose the uric acid is precipitated in crystals, but it is rapidly rendered less

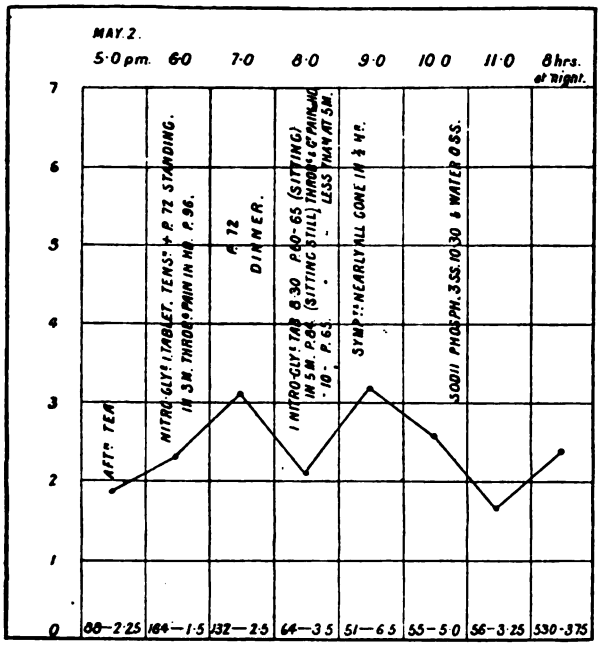

FIG. 19.—EFFECTS OF NITRO-GLYCERINE ON THE ACIDITY OF THE URINE.

soluble and is held back in certain organs and tissues in accordance with the theories of Sir A. Garrod; I shall present evidence that anything clearing the blood of uric acid frees all the capillaries and thus rapidly reduces blood-pressure, the rapidity of the fall of pressure depending on the speed and completeness with which uric acid is driven out.

In the *Lancet* (vol. i., 1891, p. 1323), it is stated that administration of sulphurous acid and even inhalation will reduce the alkalinity of the blood, which is greatly in favour of my argument and

results as to the action of nitrites, and acidity of the urine when hyposulphites or sulphur in other forms are taken. The same article states that sulphurous acid is used in preservation of wine and vegetables—a fact of importance for gouty subjects.

It is remarkable what small quantities of these acids (nitrous, sulphurous, &c.) will produce marked effects on the excretion of uric acid, nor they alone, for small quantities of salts of the mineral acids do likewise as I have observed frequently. Considering this

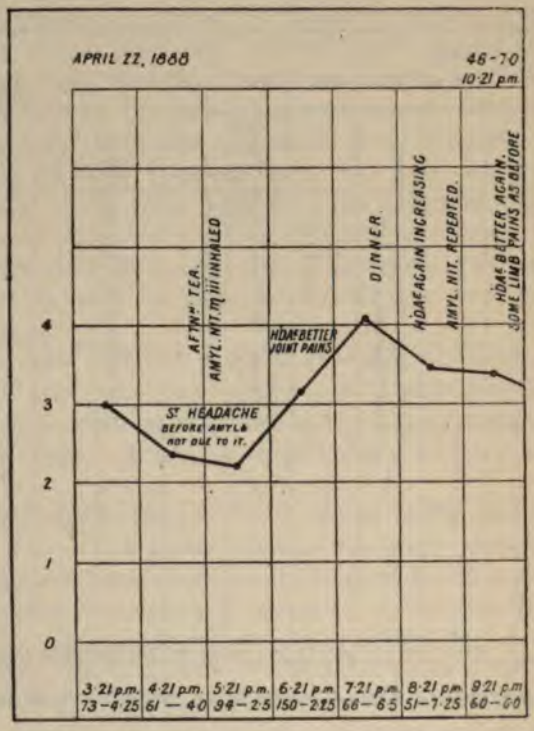

FIG. 20.—EFFECT OF NITRITE OF AMYL ON THE ACIDITY OF THE URINE.

it occurred to me that the solvent power of phosphate of soda for uric acid and urates may explain it, as it explained the difficulty with lithia. If a little lithia produces marked retention of uric acid by throwing out of action a quantity of its natural solvent, phosphate of soda, a minute quantity of acid may have the same effect on the phosphate and may change a large quantity of it from Na_2HPO_4 to NaH_2PO_4, when the effect on the solubility of the urate will be pro-

portional to the amount of phosphate thrown out of action, and not to the relatively minute amount of acid causing the change.

Hence the stimulant action of acids depends upon varying conditions in the blood and fluids; if these are favourable to diminished alkalinity they produce a large effect, if unfavourable, little or none; and thus the action of a given dose will vary not only individually, but in the same person.

The researches of the late Professor Leech (Croonian Lectures, 1893), apparently show that the nitrites exercise a direct depressant action on muscular tissue. But they are decomposed in the stomach giving off nitrous acid which is absorbed into the blood and importantly affects its composition and reaction; Professor Leech says (*Lancet*, vol. i., 1893, p. 1502), "When absorbed it (nitrous acid) is no doubt at once converted into an alkaline nitrite, for it can replace carbonic acid in its sodium compounds and convert normal sodium phosphate into acid phosphate, sodium nitrite being at the same time formed."

A rise in acidity of urine is the result of this conversion of normal phosphates into acid phosphates, and the normal phosphate of sodium being a good solvent of uric acid while the acid phosphate is not (see *Medico-Chirurgical Transactions*, vol. lxxii., p. 399), the blood ceases to hold uric acid in solution and consequently the capillaries are freed and blood pressure reduced.

It seems probable, then, that the action of nitrites on blood pressure has two causes: first, the muscular depressant action weakening the muscle fibre in the heart and the vessel walls generally (an action similar to that of tobacco, lobelia, and other depresso-motors see *Brain*, Spring and Summer number, 1893, p. 245); and second, the general freeing of capillaries produced by all substances that clear the blood of uric acid.

I was interested to hear from Captain Newland, R.A.M.C., that Dr. Saunders was using nitrites in ague to shorten the cold stage and hasten the sweating stage, apparently with good results.

There is an important note in the *British Medical Journal*, 1903, vol. ii., page 925, referring to a report by Major Jennings in the *Journal of the Royal Army Medical Corps*, on the taking of cordite by soldiers in South Africa. First occurred exhilaration, excitement, and a flow of language, doubtless the result of the great fall of blood pressure. Heavy sleep or stupor lasting from five to twelve hours supervened, and when the patient was with difficulty roused there were severe headache and muscular twitchings and protrusion of the eyes. These are symptoms of collæmia and high

blood pressure, indicating the first action of the nitrite and its rebound, thus proving that its action was largely due to its influence on uric acid; for if the blood had not been cleared of uric acid in the first stage there would have been no reaction.

If the cordite was taken with beer the intoxicating effect of the beer was increased, and the man became excited, quarrelsome, and destructive; indeed, it is stated that this combination rendered the mildest man almost maniacal. Cordite, I believe, contains 58 per cent. nitro-glycerine, therefore the result is probably principally due to this, though no doubt the other nitrous compounds would have some share.

Sir A. Garrod mentions * that he found uric acid in normal blood, and its excess in the serum of a blister in gout, and also in lead poisoning;† and shows that lead given medicinally diminishes the excretion of uric acid in the urine. He remarks:‡—"It would appear, therefore, that in individuals impregnated with lead the blood becomes loaded with uric acid, not from its increased formation, but from its imperfect excretion."

This is in complete accord with my results,§ and I apply the same reasoning to all substances diminishing excretion of uric acid in the urine. For my part I have met with no evidence that there ever has been, an excess of uric acid in the blood due to increased formation, *i.e.*, above the relation to urea of 1 to 35. I believe that for every 35 grs. of urea formed in the body, 1 gr. of uric acid is also regularly formed, but no more. The 35 grs. of soluble urea are excreted with practical certainty, but the insoluble uric acid, though in much smaller quantity, is apt from various causes, to lag behind and be retained.

We shall see later that uric acid is probably not in excess in the blood when, under the influence of lead, it is diminished in the urine, but it appears in excess when what has been held back by the lead is got into solution by alkalies or other solvents. As soon as it is in excess in the blood it begins also to pass in excess in the urine.

My investigations, I believe, prove that an excess of uric acid in the urine above the relation to urea of 1 to 35 comes from this excess, and that when the uric acid in the urine is diminished below that relation (say 1 to 45) there is little or none in the blood,

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* "Gout and Rheumatic Gout," 3rd edit., p. 84, *et seq.*

† Ibid., p. 240. ‡ Ibid., p. 243.

§ See *Med. Chir. Trans.*, vol. lxxi., p. 284.

because every particle introduced from the kidney by the renal vein. is at once caught up and stored in the liver, spleen, and other tissues.

According to Sir A. Garrod's theory, the antecedent elements of uric acid come probably from the liver to the kidney, and are there formed into urate of ammonium.

By far the largest part of the urate thus formed (say, for the sake of a definite quantity, nine-tenths) passes at once down the ureter and leaves the body; but the remaining one-tenth may, under certain conditions, pass, according to Sir A. Garrod, into the general circulation through the renal vein, and is then liable to retention in certain organs which are less alkaline than the blood, and therefore less able to hold it in solution.

It is this residue of uric acid, plus that introduced ready-formed in food which, according to my interpretation of results by the light of Sir A. Garrod's hypothesis, furnishes the uric acid of pathology. If the whole of the urate formed had passed down the ureter immediately there would be less trouble, and to ensure elimination of what is formed and to lessen the quantity introduced is the aim of treatment.

It seems probable that the alkalinity of the kidney structure partially determines how much of the urate formed shall be at once excreted, and how much temporarily kept back for eventual passage into the general circulation.

Possibly the pathological urate deposits found in the kidney after death are mere exaggerations of the normal retention occurring to some extent during life.

When urea is high and especially when it is above the physiological relation to body weight, 3 or 3·5 grs. per pound per day, it seems probable that the alkalinity of such organs as the liver, spleen and kidneys will be diminished as the acidity of the urine is increased; so that when urea is too high we shall get increased retention of uric acid in these organs (see fig. 74).

I will deal with definite quantities. If a man forms, as my results render probable, 1 gr. of uric acid for 35 grs. of urea, let us suppose that he forms in twenty-four hours 12 grs. of uric acid and 420 grs. of urea.

The whole of the urea and 10 grs. of uric acid are excreted, giving a relation in the urine of 1 of uric acid to 42 of urea; and 2·0 grs. of uric acid retained in the kidney, passing gradually into the general circulation.

In the general circulation the urate becomes insoluble and is retained in certain tissues (according to Sir A. Garrod, the liver,

the spleen, the joints and the fibrous tissues), because of their relatively diminished alkalinity and consequent deficient power of holding urates in solution.

Next day 420 grs. of urea are again formed and excreted, but uric acid is now in excess of its normal relation to urea, say 1 to 30, *i.e.*, 14·0 grs. are excreted.

According to our hypothesis only 12 grs were formed and therefore 2·0 grs. come from elsewhere, even supposing that all the uric acid formed in the kidney on this day passed direct down the ureter. It is evident that the amount of uric acid retained on the previous day furnishes just the excess in excretion of this day, and thus the excretion of uric acid, but not its formation, fluctuates daily.

It is demonstrable why excretion of uric acid is large during the "alkaline tide" of the morning, and small during the acid tide of the night hours. It is a simple question of solubility in the blood (see remarks on fig. 3).

Further, by giving alkalies the excretion can (as I have long pointed out)* be increased, or by giving acids diminished.

But if the stores in the liver, spleen, and joints have been swept out by repeated administration of solvents, no drug can cause a plus excretion of uric acid till there is fresh retention and accumulation in these structures (see figs. 7 and 8).

These facts account for all the conditions in which an excess of uric acid occurs in the body, and failure of excretion will soon retain all that is ever found before or after death.

The theories of excessive formation (*i.e.*, formation of uric acid in excess of the normal relation to urea, about 1—35) or of deficient oxidation are incompatible with these facts, and unnecessary for the explanation of disease phenomena. All the diseases discussed in this book may be prevented or cured without reference to them, and are more sensibly attributed to poisoning by meat and tea (which can be demonstrated by prevention and cure).

Sir A. Garrod points out† that there is little or no uric acid in the blood in acute rheumatism and draws the conclusion that this disease is not due to uric acid. I have given elsewhere‡ reasons for thinking this conclusion requires revision, and I shall allude to

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* See *Journal of Physiology*, vol. viii., p. 216; and *Brit. Med. Jour.*, 1890, vol. xii., p. 124.

† Reynold's "System of Medicine," 1st edit., vol. i. p. 897.

‡ *Med. Chir. Trans.*, vol. lxxiii., "Salicin compared with Salicylate of Soda," &c.

it later. My facts are in accord with those of Sir A. Garrod; it is in the conclusion that I differ from him.

One further fact about uric acid is, I believe, mentioned in all text-books of physiology, viz., it is found as a practically constant constituent of the spleen pulp after death.

It is interesting to note that uric acid is nearly always present in great excess in the urine in cases of enlarged spleen as in splenic leucocythæmia, and it is in excess in the blood in this condition.*

In several cases I examined the whole urine for eight or ten consecutive days, and in these over the whole period, the average relation of uric acid to urea in the urine was 1—12 or 1—14. It is little wonder that in these conditions excess of uric acid should be found in the blood, the excess in the urine being the index of this; in such cases a great excess of the granules precipitated in the blood by chloride of ammonium occurs, 1 to 2 and even 1 to 1 being common (see later on).

I have shown there is generally an excess of uric acid in the blood excreted during an epileptic fit (see cases in chapter vii.). Sir A. Garrod found excess of uric acid in blood drawn during an epileptic fit, and has pointed out the alternation between gout and epilepsy—a fact which my results and conclusions completely explain. And if the liver, spleen and joints are less alkaline, as Sir A. Garrod has stated, than other tissues, any uric acid coming to them in the blood stream is rendered, as he puts it, "less soluble and more easily retained;" and we can thus explain why these tissues frequently after death contain considerable quantities of uric acid.

To estimate the amount of uric acid in the blood and tissues I first made a water-extract of them by a process described by Salkowski and Leube,† and having evaporated and cleared my solution, I applied Haycraft's process, just as in the case of urine (see chapter xviii., also my remarks as to my results with this process on pp. 7 and 8).

In specimens of human blood obtained during life, I found quantities of uric acid ranging from ·03 per cent. in a case of cerebral hæmorrhage to ·0006 per cent. in a case of cellulitis, the blood flowing from incisions made into the inflamed tissue. In the blood of a fatal hæmoptysis in a case of fibroid phthisis, the patient being at the time on salicylate of soda, I found ·0065 per cent. of uric acid, and having plenty of blood to work on here I estimated the quantity more accurately than is generally possible with small samples.

* See Salkowski und Leube, *Die Lehre vom Harn*, p. 88.

† Prev. ref., p. 94.

With regard to the very small quantity of urate in the blood from incisions in an arm affected with cellulitis, Sir A. Garrod has observed ("Gout and Rheumatic Gout," pp. 187 and 274), that there is no urate in the fluid of a blister or in blood drawn directly over the inflamed joint in gout, and suggests as an explanation that inflammation destroys uric acid.

My facts are in accord with his; but I think the explanation is that local inflammation means local reduction of alkalinity, so that all urate coming to that part is rendered insoluble and retained, and the blood or serum which has passed through the inflamed part is practically cleared of uric acid. It is interesting to remember that in this condition the capillaries are very free and the capillary reflux (C.R., see chapter v.), very quick, being only one half second, or like a flash, and the explanation of this is seen in the very small quantity of uric acid in the blood from an inflamed tissue. In many inflammations of fibrous tissue throughout the body, drugs do good which reverse these conditions, bring uric acid back into the blood and slow the C. R., *e.g.*, alkalies and salicylates. A surgeon would say that the above cellulitis was due to a microbe, but it is also in a sense due to uric acid, for removal of uric acid would relieve or cure. Possibly with regard to catarrh, tubercle, and other troubles, microbe and uric acid are partners, the former failing to fructify without the latter; hence catarrh, pneumonia, cellulitis, &c., are much more virulent in those who have gout, collæmia, or Bright's disease. Certainly in acute rheumatism the urate is in the joints and the blood is cleared of it; but in gout (a more local disease) only that blood which has passed through the inflamed area is cleared of urate.

Here we have an explanation of the well-attested facts of the alternation of gout or rheumatism with headache, epilepsy, and mental depression, for uric acid attracts uric acid and where accumulations are collecting in certain joints or fibrous tissues these urate deposits tend to attract all the urate passing them in the blood, and hence perhaps for months, or even years, the blood is kept relatively clear of uric acid, and headache, epilepsy, and depression conspicuously absent.

This also explains the fact that inflammation increases combustion (everything clearing the blood of uric acid does this), for inflammation clears the blood of uric acid locally very completely and to some extent generally. This clearing up of collæmia, this quickened circulation and increased combustion diminishes, as we shall see later on, albuminuria and glycosuria, the products of im-

perfect combustion, and increases instead the products of more complete combustion, for the same reason that every fall of uric acid causes a rise of urea.

In specimens of human blood obtained after death from the heart cavities, it seemed to me that when the joints contained urates there was more in the blood than when they contained none—thus eleven cases with urate deposits gave ·03184 per cent. of uric acid in the blood, and eleven cases in which there were no urates gave an average of ·02255 per cent.

I noticed that in the blood of cases dying of pneumonia there was generally a great excess of uric acid, and five cases of this kind gave an average of ·03742 per cent.; but in a case of pneumonia and delirium tremens the blood obtained by venesection while the temperature was 102°, only contained ·0006 per cent., and this fact explains the great excess met with in the blood of these cases after death.

During the high fever of the first two or three days of a pneumonia, there is a great rise of acidity or, what amounts to the same thing, a fall in the alkalinity of the blood and tissue fluids, and this drives all the uric acid out of the blood and retains it in considerable quantity (for the reasons previously given) in the kidney, liver, spleen, and possibly the joints and other tissues. There it remains so long as the fever diminishes the alkalinity of the blood and tissue fluids; but when dyspnœa increases or temperature falls, the alkalinity of these fluids rises and the retained uric acid is drawn into solution, thus coming to be in excess in the blood and passing in excess in the urine; the excess of uric acid in the blood accounting for the headache, mental depression and suicide, with slow pulse, high blood pressure and subnormal temperature, so common in convalescence from acute febrile diseases.

If, however, the patient dies the same thing occurs. For some hours before death there is a failure of nutritive processes; and even if the temperature keeps up, the alkalinity of the blood and fluids will rise owing to failure of nutrition and of respiration. Hence uric acid is dissolved from its deposits and is in excess in the blood at the time of death, this excess being understood as the direct result of its expulsion from the blood and retention in certain organs during the diminished alkalinity of the early stages of the acute fever.

Cases in which at the time of death temperature was high and rising, as in meningitis, yield generally only a small amount of uric acid in the blood; but there are several exceptions to this rule, due probably to the fact that in spite of high temperature the alkalinity

of the blood and fluids may be rising just before death, owing to general failure of nutrition. In one case of pyæmia with embolic hemiplegia I got quite a large amount (·05426 per cent.) in the blood, in spite of a temperature rising to 104° at the time of death; and in another case of cerebral lesion about the same amount. In cases of this kind I suggest that the cerebral changes (softening) in connection with the hemiplegia cause the passage of a large amount of phosphates through the blood;* and that, as I have pointed out,† certain phosphates of soda, potash, and ammonia are powerful solvents of uric acid and greatly increase its excretion, and doubtless its quantity in the blood for the time being.

Two cases, in which the blood contained ·01243 and ·0588 per cent., had ·06384 and ·08668 per cent. = 4·5 to 6·1 grs. per lb. in the spleen respectively, the relative excess in the spleen being in accord, as previously mentioned, with everything already known on the subject.

Nine cases of morbus cordis gave an average of ·0335 per cent. in the blood after death.

For the rest my results show that the blood after death generally contains some little uric acid though the amount is subject to considerable variation, the largest quantity met with being ·0744 per cent. in a case of pneumonia, and the smallest ·01008 per cent. in a case of meningitis.

Eight specimens of liver yielded an average of ·05928 per cent., = 4·2 grs. per lb., and the liver of a six months' fœtus that did not survive its birth yielded ·003 per cent. = ·2 grs. per lb.

Five specimens of spleen yielded an average of ·06412 per cent. = 4·5 grs. per lb., or slightly more than the liver.

Nine specimens of kidney yielded an average of ·0513 per cent. = 3·6 grs. per pound, that is, less than either the liver or spleen. One kidney (not included in the above) from a child thirteen days old, which contained well-marked uric acid infarcts, yielded the very large quantity of ·23 per cent. = 16·4 grs. per pound, or more than four times as much as the above specimens. My thanks are due to my colleague, Dr. S. W. Wheaton, who placed this interesting specimen at my disposal. He informs me that the uric acid of these infarcts, which were plainly visible in the medulla of the kidney, was seen under the microscope to be both in the tubules and in the connective tissue round them, which, according to authorities on the

* Zuelzer, "*Semiologie des Harns*," p. 89; and *Brain*, vol. ix., p. 364.
† Fig. 7, and *Med. Chir. Trans.*, vol. lxxii.

subject, is generally the case (see Zeigler, *Pathologische Anatomie*, vol. ii., p. 333). The kidney of the above-mentioned six months' fœtus contained ·002 per cent. = ·14 grs. to the pound.

A piece of human psoas muscle contained apparently ·028 per cent. = 2 grs. to the pound. It may be interesting to mention here that half a pound of beef-steak yielded ·019 per cent. = 1·3 grs. to the pound, and that I found the equivalent of ·697 per cent. = 49 grs. to the pound, in some meat juice, and of ·883 per cent. = 63 grs. to the pound, in some meat extracts (see also chapter xvii. and remarks on these quantities).

In a case where the blood from the heart had ·06904 per cent. (a very large quantity), the urine drawn from the bladder gave a relation of uric acid to urea of 1 to 9·4, a great excess also. In a case with ·02384 per cent. in blood, the relation in the urine was 1 to 27, *i.e.*, much less in both. In another case there was ·03024 per cent. in blood, and relation in urine 1 to 29. And in another, ·03914 per cent. in blood, and urine relation 1 to 10, *i.e.*, a considerably greater excess in the urine than in the blood.

In another case ·06888 per cent. in the blood, and a relation of uric acid to urea in the urine found in the bladder of 1 to 18, and the percentage of uric acid in the urine was ·03696. The liver in this case contained ·088 per cent. = 6·3 grs. per pound. The amount in the spleen was not estimated, but no doubt, as in other cases, it contained nearly as large an amount as the liver. These facts seem to me to be strongly in favour of my argument that the excess in the urine is an overflow from an excess in the blood, and that the excess in the blood again is due to its dissolving and taking up some of the stores in liver and spleen.

For some interesting facts concerning the origin and experimental production of uric acid infarcts, see Dr. E. Schreiber, *Zeitschr. für Klin. Med.*, 38 Bd., H. 4, 5, 6, where it appears that two factors are necessary (1) excess of uric acid, and (2) some irritation in the kidney, the latter, doubtless, diminishing its alkalinity and rendering its tissue fluids bad solvents of uric acid (see chapter xiii.).

A similar explanation applies to the greater quantity of uric acid in the blood of cases with urates in their joints; here the blood has obviously an additional storehouse from which supplies of uric acid can be drawn. And in cases of chronic wasting disease it is demonstrable that supplies are thus drawn and that for weeks together there is an excessive excretion of uric acid in the urine, while after death erosion of joints is found, with all or nearly all the urate dissolved out.

These results show that when there is excess in the blood there is also excess in the urine, but we must not press the matter more closely, or we shall get into difficulty.

We must remember that the urine found in the bladder after death is the excretion possibly of several hours during which the amount of uric acid in the blood fluctuated considerably, so that nothing more than a general rough relation between the two can be expected. It is not a little remarkable that in upwards of sixty specimens of *post-mortem* blood examined by me, it should have been possible to group the diseases causing death in accordance with the amount of uric acid or xanthin found. Thus a specimen containing a very large quantity might come from a case of pneumonia or cerebral hæmorrhage, one with moderate quantity from a case of any wasting disease (especially if with urates in the joints) while one with a very small quantity would probably come from a case of meningitis or other disease accompanied by acute fever to the time of death. In thus fluctuating with the presence or absence of fever in the hours preceding death, this substance (uric acid or xanthin) in the blood obeys the laws that govern the excretion of uric acid in the urine during life. It also corresponds definitely with the excretion of uric acid in the urine just before death, and this may be linked with what I shall point out later, that the swallowing of any xanthin compound increases the excretion of uric acid in the urine.

The granules precipitated in the blood by chloride of ammonium, (mentioned later) tell the same tale, for they are scanty in fever and more numerous in conditions of debility and wasting disease and after a fever.

Having had my attention drawn to the matter by my friend, Captain E. Roberts, R.A.M.C., I examined a collection of cataractous lenses kindly sent by my colleague, Mr. Holmes Spicer, by the same process as in the case of the above organs and tissues, but was unable to find any trace of uric acid. Captain Roberts tells me it has been found by some observers but it seems that the cataracts we see in this country associated with feeble old age are more likely to be connected with the circulation changes of collæmia, other signs of which are often so marked in the aged, rather than with the uratic arthritis which comes at an earlier and more vigorous period of life; whereas in feeble old age the urates are removed from the joints rather than deposited, the blood being then a good solvent.

I have also made a few examinations of the blood and organs of animals.

Dog killed after operation under chloroform: blood contained

·00168 per cent. That of another dog ·00336 per cent., and the urine of this dog obtained at the time of death gave a relation of uric acid to urea 1 to 85, which is a large amount of uric acid for a dog.

The urine of a cat gave a uric acid urea relation of 1 to 110.

The blood of several other dogs contained very small traces, about ·00126 per cent.; their livers from ·04 to ·02 per cent., and their urine at the time of death gave uric acid urea relations of 1 to 136 to 1 to 144.

I then tried to work on the urine of a single animal (dog), collecting it daily, and endeavouring to alter the uric acid urea relations by diet and drugs.

A bitch, weighing 11 lbs., was kept in the ordinary form of cage for collecting the urine, and was fed on 6·6 oz. boiled horse, 5 oz. milk and 5 oz. of water.

The urine was passed at very irregular intervals, but the uric acid urea relation was 1 to 87 on the first day, and 1 to 165 on the fifth and last day of the above meat diet; urea being 25 grs. per lb. So that it rather appeared that the meat diet in the dog, as in man, diminishes the excretion of uric acid at first.

The animal was then put on a diet of porridge (one pint and milk one and a half pints), which, however, it took very badly; on this urea fell to 13, and eventually even to 5 and 6 grs. to the lb., and uric acid increased relatively, being 1 to 146, 1 to 110, and 1 to 98.

On the last day of this experiment I gave hyposulphite of soda in the milk with the object of diminishing the uric acid, and apparently with some success, as the relation altered to 143.

The animal, which now weighed 13 lbs. (an increase of 2 lbs.), was killed, and the blood, liver and kidneys examined.

The blood contained		·0003	per cent.
,,	liver	·0287	,,
,,	kidneys	·0460	,,

The very small quantity in the blood was in accordance with the diminution in the urine, and this was probably due to the drug given, which corroborates what I have said as to the general correspondence between the quantities in the blood and urine.

It is to be observed in reference to the question of formation *v.* introduction, that this bitch probably formed absolutely no uric acid, for as she excreted 25 grs. of urea per pound, or 275 grs. a day, and uric acid in about the average relation to it of 1 to 120 or 2·2 grs., the whole of this might have come from the meat eaten, for

if there is as much uric acid in horse as in beef (see chapter xvii.), 6·6 oz. of horse-flesh would supply 2·4 grs. of uric acid, and it thus seems that all the uric acid in the urine of these carnivora may be due to introduction.

In other dogs I attempted to increase the uric acid in the blood and urine by giving salicylate of soda, but this failed completely. There was practically no uric acid in the blood of either of the two animals thus treated, nor was there any increase of uric acid in the urine, the relation being in this latter fluid 1 to 140 to 1 to 150. Both urines gave a strong salicin reaction with perchloride of iron, so that the drug was plentifully absorbed and excreted.

It is a very interesting fact, that salicylate of soda, which has such a great power over the excretion of uric acid in man, should produce absolutely no effect on it in dogs.

I see my way, however, to some explanation of the fact, for in all I have written about the action of salicylate of soda in man, I have always been careful to point out that acids aid, and alkalies hinder, its solvent action on urates (see p. 43 and fig. 71). Strange as it may seem, the acidity of dogs is very low indeed; and the bitch fed on horseflesh, though excreting 25 grs. of urea per lb., only excreted acid to the equivalent of 1 gr. of oxalic acid for 16 to 17, or even 18 grs. of urea, the acidity urea relation being 1 to 18; whereas in man, as I have shown in my own case, it is 1 to 6·8. Therefore this dog (a carnivore) excreted only one-third of the acid per grain of urea that man does, and probably its blood was far more alkaline than that of a man on the same diet, therefore the the salicylate failed to affect the uric acid as it does in man (see also cases in chapter xvi.).

With regard to the relation of acidity to urea, Dr. A. Auerbach has pointed out (*Virchow's Archiv.*, vol. xcviii., p. 512) that no amount of acid will render the blood of carnivora acid, as they form ammonia to neutralise the acid. No doubt something of the sort accounts for the low acidity in the dog above mentioned.

The fact that man is devoid of this power of forming ammonia to neutralise acids (or has it only to a very slight extent as compared with the carnivora) is, I think, a further proof that he is physiologically a frugivore (for further differences between men and carnivora, see "Diet and Food," ed. vi., p. 86).

In two monkeys, the organs of which were kindly placed at my disposal by Dr. H. H. Tooth, I found in the blood about ·00441 per cent. = ·3 grs. per lb., in the liver ·060 per cent. = 4·2 grs. per lb., in the kidneys ·050 per cent. = 3·5 grs. per lb., and in the muscles

of the back ·017 per cent. = 1·2 grs. per lb. of uric acid or xanthins (here, just as in man, the kidneys contain less than the liver).

With my results it may be interesting to mention those of a well-known author, Professor R. v. Jaksch, of Prague, who in a paper, "Ueber uricacidæmie" (*Deutsch. Med. Wochenschrift*, Aug., 1890, p. 741), gives his investigations into the uric acid in the blood, with an explanation of the causes that tend to increase its quantity.

His facts in the main agree with mine; but his conclusions are based on what I believe to be the erroneous theory, that all increase of uric acid in the blood is due to deficient oxidation, and not, as I have endeavoured to show, to a retention in the body, together with daily introduction, leading to subsequent increased excretion, the increase passing through the blood on its way to the kidneys.

Professor v. Jaksch states that he found no demonstrable uric acid in the blood of nine healthy individuals, and the same in cases of tabes, multiple sclerosis, polyneuritis, and cerebral tumour.

I should have expected that if there was any wasting in the diseases mentioned there would have been some uric acid in the blood, but as all the facts are not given, it is impossible to draw any definite conclusion.

To reason from the results in healthy subjects, the time of day at which the blood was drawn should be given; for my researches make it probable that there is some appreciable amount of uric acid in the blood of every one for an hour or two during the "alkaline tide" of the morning (fig. 3, also 52, and remarks on it), and that the excess in the urine common at this time is an overflow from some excess in the blood. The mental condition, the capillary reflux, the blood pressure and the rate of the pulse, the temperature and other things, often point to excess of uric acid in the blood during the "alkaline tide."

Again in nine cases of typhus, Professor v. Jaksch found no uric acid in the blood; but it was present in one case after the fever had ceased. Similarly in intermittent fever there was no uric acid during the fever; but, when the temperature fell, uricacidæmia or collæmia supervened, just as my researches on blood granules, to be mentioned presently, show.

This is in complete accord with my results and reasoning. When there was fever the alkalinity of the blood diminished, the uric acid became less soluble, and was retained in the liver, spleen, joints, &c. (see previous remarks about fig. 5). The enlargement of the spleen in malarial fevers has an interesting relation, as I shall point out, to the amount of uric acid that can be retained in the body in this

disease, and others in which the organ is enlarged. I have found the spleen, as above shown, to contain about 4·5 grs. per lb.; so that obviously a spleen weighing 6 to 8 lbs. would contain 27—36 grs., and if this organ is alternately filled and emptied in the alternations and remissions of fever, we shall account for all the uric acid so often found in excess in some part of the body in these cases. Again, if we reflect that the holding back or retention of little more than 1 gr. a day (that is to say, if the formation plus the introduction of the 24 hours exceed the excretion of the same period by one grain, and it is easy on any given day to produce a retention to this extent with drugs) will furnish 1 oz. of uric acid in a year, we shall account for all that is ever met with after death, whether in the joints, viscera, and tissues, or in the urinary passages in the form of calculi.

On the fall of temperature the alkalinity of the blood increased, and it dissolved the uric acid from its places of deposit; had the urine been examined at the same time, corresponding changes in the quantity of uric acid excreted would have been observed, and the amount of urinary water and rate and tension of the pulse would show concomitant alterations corresponding to the effects of uric acid on the capillaries (see fig. 42).

In diseases of the liver, intestines and stomach, there was only collæmia when they occurred with anæmia. I should read for anæmia wasting and debility, with as their result a diminished excretion of urea and acid, and a consequent fall in the acidity of the urine and increase in the alkalinity of the blood. Among heart diseases he observed that those with most cyanosis had most uric acid in the blood.

Again, he often found uric acid in the blood in diseases of the lungs and pleuræ, emphysema and exudations.

It was constantly present in considerable quantity in five cases of pneumonia, even during the febrile stage.

The explanation of these results in pneumonia, apparently in opposition to my result, will be discussed. The blood, in the single case I was able to examine, was drawn early in the acute stage of the disease, and it must be remembered that working on *post-mortem* blood I found an extremely large amount of uric acid in cases of pneumonia.

None in six cases of rheumatic fever.

A considerable quantity in kidney diseases of different forms—ten cases.

From these results he reasons that the blood contains much uric acid in cases of primary and secondary anæmia.

That it is present in the blood in considerable quantities in other diseases besides gout;

That it does not take part in the acid intoxication of fevers, since fever is unfavourable to the presence of uric acid in the blood;

That in dyspnœa and cyanosis the more the blood is overloaded with carbonic acid the more uric acid it contains. Hence in pneumonia, collæmia may occur in spite of fever.

And lastly, he concludes that it is plus in nephritis and anæmia, because the red cells are unable to further oxidise the uric acid, and hence everything that interferes with the oxygen-carrying power of the red cells causes excess of uric acid in the blood.

This appears a plausible conclusion, but my researches on the excretion of uric acid throw considerable doubt on its validity, and we shall, I think, see that all excess of uric acid in the blood is *the cause* of defective interchange between the blood and the tissues, and therefore of defective nutrition and combustion; and that the cause being removed the effects are absent.

It is known that the excretion of uric acid is large in the morning when the acidity of the urine is low, in what the late Sir W. Roberts has named the "alkaline tide."

This has been regarded as due to a plus formation of uric acid during these hours; but I have shown that the excretion of uric acid can be altered in either direction at any time. The natural plus excretion of the "alkaline tide" can either be increased or diminished. If increase is desired this can be done by retaining a little uric acid in the body by acids given on the previous day, and increasing the alkalinity next morning with a dose of alkali. If it is to be diminished an acid to counteract the alkali of the "alkaline tide" must be given; or the most easily available uric acid stores must be removed on the previous day by giving a powerful solvent, as salicylate of soda, when the "alkaline tide" next morning will have nothing to act upon and there will be no plus excretion of uric acid. Anyone who will give a few drugs and watch the results, may easily convince himself that the excretion of uric acid can be varied at pleasure in either direction (see also blood pressure and circulation curves in chap. v.).

In illustration of this I refer again to fig. 8. It may there be seen that a dose of 15 grs. of the salicylate taken three times daily for five days, produced at first a very large excretion of uric acid. Next day, the drug being continued as before, it fell close to the urea again; on the two following days (4 and 5 in the figure) it rose a little, but to nothing approaching the height of its rise on the first

day under salicylate (day 2 of figure). On day 6, the last day of salicylate, it came still nearer the urea; and on day 7, when salicylate was stopped, it fell far below the urea, and remained there as my curves (not given in the figure) show, for the three following days.

All curves of uric acid excretion under salicylate show practically the same thing, and it is seen in the excretion curve of acute rheumatism treated by this drug (see fig. 68), only that the quantities are greater. In all cases excretion reaches its highest point on the first or second day, and the same height is never again attained, however long the drug is continued. On the contrary, the excretion shows a tendency, with a few oscillations, to come down to the level of urea and remain there; and if the drug is stopped it falls far below the urea and remains there for several days.

My explanation is, that on the first day the salicylate meets a considerable amount of uric acid in the joints, liver, spleen, &c., on which it can act; that as it dissolves this and passes the greater part into the urine, it never subsequently meets with so much on which it can act, hence the curve is never so high again. Afterwards a little is introduced, or here and there comes within its range of action, but each day there is less and less, so that the curve approaches the urea curve, which is the level of formation.

When the drug is stopped there is at once a retention of uric acid (day 7), replacing to some extent what has been removed from the organs and tissues by the solvent.

If on day 2 an alkali were given instead, it would produce a plus excretion of uric acid; but the same dose of alkali given on day 7 would fail to raise the uric acid above the urea; the more powerful solvent salicylate removes so much uric acid that the alkali has nothing to act upon. It will now be understood that by thus giving drugs, and watching their effects, if need be, from hour to hour, it is no difficult matter to alter the excretion of uric acid in any required direction.

The plus excretion of the "alkaline tide" is, therefore, a single instance of a rule which may be thus stated:—All substances increasing the solubility of uric acid increase its excretion (provided there is some uric acid in the body for them to act upon; in myself, for instance, a solvent produces a much smaller excretion than if given to a man who is saturated with uric acid), and all substances diminishing the solubility of uric acid diminish excretion and cause it to be retained in the body. If the normal plus excretion of uric acid in the "alkaline tide" were due to plus formation, why should the previous removal of uric acid diminish it, or the previous storing of uric acid increase it?

I have given my reasons for believing that every plus excretion of uric acid in the urine is simply the overflow from an excess in the blood, and that when there is a diminished excretion in the urine there is none, or almost none, in the blood. In other words, the amount of uric acid in the urine in relation to urea is the index of the amount in the blood, and in altering the amount in the excretion we of necessity alter at the same time the amount in the circulating fluid.

The results published by Professor v. Jaksch will presently be seen to be simple instances of the action of the law of solubilities above stated.

I can show that alkalies, phosphate of soda and compounds of salicylic acid increase excretion of uric acid in the urine, and for a time also increase the amount in the blood. Conversely, acids, lead, and other substances mentioned, diminish the solubility of uric acid, diminish its excretion in the urine and its amount in the blood. That acids, iron, and lead interfere with the solubility of uric acid is well known, and lithia, as I have pointed out elsewhere,* though said to be a beautiful solvent of uric acid in a test tube, yet when given to the human subject by the mouth never reaches the uric acid at all, because it forms an insoluble compound with the phosphate of soda in the blood, thus removing one of the natural solvents of uric acid, and diminishing its power of holding uric acid in solution. In accordance with this it diminishes the excretion of uric acid in the urine and the amount contained in the blood; and as a result it has the same effect on the rate and tension of the pulse, the flow of urine, and the circulation of the brain (as evidenced by the mental condition), as acids, iron, and lead, though acids raise the acidity of the urine and diminish the alkalinity of the blood, while lithia lowers the acidity of the urine and increases the alkalinity of the blood; thus demonstrating that the pulse rate and tension and the circulation in the various organs mentioned are not directly affected by the drugs, but only indirectly through their effects on the solubility of uric acid and the amount of this which the blood can hold in solution.

In ordinary circumstances a dose of potash or soda increases the excretion of uric acid in the urine, and also increases the amount in the blood; as a result it will slow the pulse, raise the tension, and produce mental depression and scanty urine from its effect on the circulation of the brain and kidney respectively; but if all available

* *Med. Chir. Trans.*, vol. lxxi., p. 287.

uric acid has been cleared out of the body by giving a salicylate for two or three days beforehand (see fig. 8), a dose of soda or potash will produce no plus excretion of uric acid in the urine and no excess in the blood; none of the above-mentioned vascular phenomena will make their appearance, and the circulation in the brain and kidney will go on unhindered; thus proving beyond all doubt, that these vascular phenomena are due, not to the direct action of the drugs used, nor to the greater or less alkalinity of the blood *per se*, but to the larger or smaller amount of uric acid which it can hold in solution. The blood granules now tell us the quantity in the blood stream, and the capillary reflux indicates its effect on the circulation, so that the quantity of uric acid in the blood can be fixed approximately in half a minute. We shall see in chapter viii. that the varying amount of uric acid in the blood determines the presence or absence of fatigue, and the rise or fall of urea as the result of exercise; and we have already seen (fig. 5) that it affects the distribution and the production of heat.

I think, therefore, that the connection traced by Professor v. Jaksch between deficient oxidation and excess of uric acid in the blood is correct as regards the facts, but the explanation probably differs from his own.

Dr. Peiper, whom v. Jaksch quotes, points out that the alkalinity of the blood is diminished in all fevers, except when they are complicated by dyspnœa and cyanosis.*

This is a most important exception, and on further investigation it will, I think, be seen that it furnishes an explanation of most of Professor v. Jaksch's facts.

It may be worth while to enquire why dyspnœa and cyanosis (that is, deficient oxidation) should prevent the diminution of the alkalinity of the blood which occurs in fever.

The word oxygen itself supplies an explanation, as its derivation, ὀξύς, acid, and γεννάω, I produce, gives a clue.

It is extremely probable, indeed almost certain, that oxygen in the human body acts just as in the chemical laboratory, and when it oxidises certain substances it produces compounds of an acid nature, and that form of energy which we call heat.

I know as a fact that when certain compounds of sulphur are given by the mouth, themselves having a neutral reaction, there appears as marked a rise in the acidity of the urine, as if a very strong dose of acid had been given, and this goes on for some

* *Virchow's Archiv.*, June, 1889, p. 337.

little time (see fig. 11). I believe there is scarcely room for doubt that this is due to the oxidation of the sulphur with the formation of some acid.

It is extremely probable that in the ordinary metabolism of the human body the same thing occurs, and oxygen combines with certain elements in the food or tissues, *e.g.*, the phosphorus or sulphur of the albumen molecule, to form, as in the laboratory, heat and acids; in fever the same processes are enlarged and result in a rise of body temperature and an increased formation of acids, causing a rise in the acidity of the urine and a fall in the alkalinity of the blood (see also chapter iv.).

But if oxygen is deficient, as in dyspnœa or cyanosis, the chemical changes are altered, the temperature does not rise so high, and there is a lessened formation of acid; hence, as pointed out by Dr. Peiper, the alkalinity of the blood is not diminished.

If, then, with regard to the amount of uric acid found in the blood by Professor v. Jaksch, we read for deficient oxidation, *deficient formation of acids*, we are in a position to explain his results; since the excess of uric acid found in the blood in all conditions of diminished oxidation can be accounted for by my law of solubilities.

In ordinary fevers increase of oxidation diminishes the alkalinity of the blood and reduces almost to *nil* the amount of uric acid held in solution; a complete explanation of the results of Sir A. Garrod in acute rheumatism, and the concordant results of Professor v. Jaksch and myself in fever and inflammation, which the blood granules and the capillary reflux agree in confirming.

But if there is a deficiency of oxygen the acids are not formed, the alkalinity of the blood is not diminished—it may even be increased; and its solvent power for uric acid being thus undiminished or increased, it at once takes up a large amount in solution, and there is a corresponding increase in the uric acid of the urine. Hence also in conditions of dyspnœa the blood granules are numerous, the capillary reflux slow and blood pressure high, in spite of some fever.

Precisely the same changes in the amounts of uric acid in the urine and blood can be produced by giving alkalies and acids respectively.

There is, therefore, no reason to believe in the existence of an excessive formation of uric acid, and all fluctuations in excretion can be explained by its simple retention, and what Sir A. Garrod says of lead (previous quotation) is probably true of all substances affecting excretion of uric acid in the same way.

Practically, in the human body uric acid is always formed in a definite proportion to urea, about one grain of uric acid for 30 or 35 grains of urea; and I have given above some reasons for this statement. Sir A. Garrod* sought to explain this fact by suggesting that certain cells in the kidney formed urea, and certain other cells, having a definite numerical relation to them, formed uric acid; but I believe that a satisfactory chemical explanation of the relative formation of these two substances may yet be forthcoming.

Thus all Professor v. Jaksch's results refer to excretion of uric acid, and have nothing to do with formation; and his interesting observation on the relation between anæmia and excess of uric acid in the blood, which agrees so completely with my own as regards the facts, is made the foundation for an erroneous inference, for my researches further on indicate that he has inverted the truth, and that instead of the deficient oxidation of anæmia causing excess of uric acid, this excess causes anæmia.

As regards the presence of uric acid in the blood, Mr. Barker Smith has stated (*Medical Times and Hospital Gazette*, September, 1896), that with chloride of ammonium as a precipitant he obtained microscopic evidence of the presence of uric acid or urates in urine diluted so as to contain about one per forty thousand of these substances, and this led him to examine the blood for similar microscopic evidence of urates, with apparently positive results.

His directions read: "Prick the finger with a needle and obtain a droplet of blood, touch it with the cover glass, then with the needle add a minute portion of carbonate of soda solution, and then a similar portion of sal ammoniac. Mix together and examine under a fourth or fifth object glass after half-an-hour."

The solutions used appear to be sodii carb. 10 per cent., and ammon. chlor. 20 per cent.

He further says, "Granular urates may be seen distinct from micrococci and from albocytes; some appear in the blood corpuscles."

In subsequent writings he acknowledges that the granular urates have to be distinguished from granules thrown down by the solutions used, as well as from micrococci and albocytes.

It soon occurred to me that having, as I believe, almost absolute power over the quantities of uric acid in the urine and in the blood,

* *Brit. Med. Journ.*, vol. i., 1883, p. 547.

it would not be very difficult to put these statements to such tests as would settle the question of their value.

What I had to distinguish these possible urates from were, (1) micrococci, (2) albocytes, and (3) granules from the solutions used.

It appears probable that by using as far as possible constant and small quantities of the solutions, the last may be averaged and neglected, and as regards albocytes and micrococci there is no reason to suppose that they will vary constantly with the uric acid present; while if the granules are found to vary constantly with the amount of uric acid in the urine in health, and with what is known as to its presence in the blood in disease, we may similarly neglect albocytes and micrococci.

Now uric acid is present in the urine in large amount during certain hours of the day, and in very small amount during certain hours of the evening and night, and it can be made to vary in the urine at any time by many drugs; I have also given my reasons for believing that every such artificial or natural variation in the excretion in the urine is the index of a similar variation in the quantity in the blood.

If this is true, and the granules pointed out under the microscope by Mr. Barker Smith are urates, or xanthins (for xanthin also appears to be precipitated by chloride of ammonium), they should vary in quantity, with the normal urinary excretion of uric acid in physiological conditions, with the artificial alterations in excretion produced by drugs or feeding with uric acid or xanthins, and with the best attested pathological variations in the amounts of uric acid in the urine and blood.

I accordingly examined my own blood night and morning, taking it in the morning at some hour between 6 a.m. and 9 a.m., when uric acid is above urea, and comparing this with 10.30 or 11 p.m., when uric acid is below urea (fig. 3). There were always many more of these granules present in the morning than in the evening. Thus, in the morning it was no uncommon thing to find granules present in the relation of one to every eight, ten, or twelve red cells, while in the evening the relation was one to fifteen, twenty, or twenty-five.

Then one morning, when I had all the signs of collæmia and high blood pressure after a rather indigestible supper, I examined the blood, and finding more granules than usual, I took a dose of calomel and watched the urine half hour by half hour, and when a diuresis came (the urine rising from about 35-40 cc. in an hour up to 70 cc. in the same time) I examined the blood again and found a much smaller number of granules.

It seems to me unlikely that either albocytes or micrococci could so regularly vary with the time of day, and as to the solutions, they were used in the same way each time, and it is hardly likely that any granules from them could account for such constant variations. Besides, any natural blood elements would be more numerous after a diuresis than before it, but it was just the reverse with these granules.

I then considered pathology, and subjected the matter to the severest test possible.

There is no fact more generally agreed upon by workers on uric acid than this, that if excess of uric acid is found in any blood, it is in that of a patient who suffers from chronic gout, more especially if it is conjoined with chronic Bright's disease; and it would be further agreed that for a blood almost completely free from uric acid you had better examine a patient suffering from acute fever, Sir A. Garrod and Professor v. Jaksch having pointed out that uric acid is absent under these conditions.

I accordingly took the blood of a patient suffering from acute pulmonary disease with a temperature above 102° F., and I prepared for comparison a similar specimen of blood from a case of chronic gout with chronic Bright's disease.

The result was absolutely conclusive; a single glance down the microscope sufficed, for the blood of the febrile patient contained comparatively few granules less than my own; while that of the gouty patient contained an enormous number, three or four times as many as I had ever seen in my own; indeed, I believe the relation of granules to blood cells in this gouty blood was practically one to one. I repeated my examination, and always found more in this patient's blood than in any I had examined.

I then produced an artificial increase of the uric acid and xanthin in my blood by swallowing some small quantities of theobromine, and again the granules seemed to increase or diminish with the uric acid in the urine.

Thus, one day when the uric acid urea relation in the urine was one to twenty-six, and when 3½ grs. of uric acid passed through the blood, I examined it at 4.50 p.m., when there was fairly marked mental depression, and found granules in the relation to red cells of one to four; and on this afternoon my blood could not at once be told from that of the gouty patient, and it was only on carefully counting with a micrometer eye-piece that his blood was found to give a relation one to three or even one to two.

On the following day at the same hour I again examined my

blood, there being no mental depression, the relation of the uric acid to urea in the urine of the day being one to thirty-six. In this blood I found relations of one to sixteen and one to eighteen, and it could as on other occasions be easily distinguished from that of the gouty man.

Further experience led me to modify Mr. Barker Smith's process to some extent. Thus I take a very small drop of blood on a microscope slide and mix with three or four times its volume of each of the solutions, since dilution facilitates counting. After mixing well I put on a cover glass and place the slide in a box or under a glass, with some moist blotting paper or cotton wool to prevent evaporation, that there may be little or no increase of granules from the solutions. In half an hour I examine under the microscope, choosing a field near the centre of the cover glass, that is, as far from the effects of evaporation as possible. I then count all the granules in a field and then all the red cells in the same field, and repeat this three or four times, adding the results; the total of the granules divided into the total of red cells gives me the average relation of granules to cells. To facilitate counting the red cells I use a micrometer eye-piece, and count the red cells only in a fraction of the field and multiply.

By this process I found that I got absolutely constant results, and that there could be no question as to albocytes or micrococci, for it was impossible to believe that either of these could vary as I found these granules do in constant relation to the excretion of uric acid in the urine, whether in its daily physiological fluctuations or in those of drug action or pathology.

It was evident that as I had practically absolute power over the excretion of uric acid in the urine, so I had also absolute power over the number of granules in the blood.

As my results can be reproduced easily, I shall not devote space to an account of the whole of my research, but shall mention a few typical instances of the relations of granules to red cells in physiology, drug action and pathology.

Indeed, since I found that the results were constant and reliable I have ceased to collect them.

After watching the morning and evening results in physiology in my own person for some time, I concluded that I should probably get distinct results by examining both blood and urine from hour to hour, and fig. 21 shows a result thus obtained.

The broken line shows the total hourly excretion of uric acid in the urine in fractions of a grain, the continuous line shows the

relation of the granules to red cells in the blood at one moment in the hour 10.15 to 11.15, and so on, the blood being drawn just after the urine had been passed, and the blood results were tabulated before the uric acid was estimated in any of the samples of urine.

In this figure we see that at 10.15 a.m. the hourly excretion of uric acid was 0·49 grs., while the relation of granules to red cells was 1 to 8. At 11.15 the uric acid excreted in the hour was 0·34 grs., and the blood granules 1 to 17. At 12.15 the uric acid was 0·29 grs., but the granules had risen to 1 to 10. At 1.15 the uric acid had risen to 0·44 grs., but the granules had fallen to 1—15. At 2.15 the uric acid had fallen to 0·35 grs., but the granules were not examined. Considering the figure one is struck by the similarity of the two curves, and if we could move the granules' curve about an hour to the right they would be almost absolutely parallel. In other words the changes in the granules in the blood preceded by

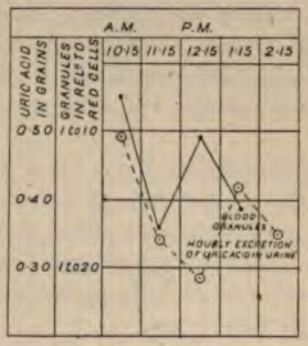

FIG. 21.—CURVES SHOWING THE RELATION OF THE NUMBER OF GRANULES IN THE BLOOD TO THE EXCRETION OF URIC ACID IN THE URINE HOUR BY HOUR.

about an hour corresponding changes in the excretion of uric acid in the urine. Thus the lowest point in the granules is at 11.15, the lowest in the excretion curve is at 12.15; the granules show a rise at 12.15, the excretion shows a rise at 1.15; the granules show a fall at 1.15, the excretion shows a fall at 2.15.

This is a fairly constant characteristic, so that I have said from my similar results that the changes in the blood granules precede the corresponding changes in the excretion by from 30 to 90 minutes. The larger the change in the granules the more marked the corresponding fluctuation in the excretion, but we must expect a certain small amount of variation where the changes are less marked, for the excretion is the total result of a whole hour,

while the granules represent the condition of the blood only at one moment in that hour.

The blood of children generally contains more granules than that of adults (say, for instance, 1 to 6 in the morning and 1 to 12 in the evening, just as their urine generally contains more uric acid, and as they excrete more daily or hourly for each pound of body weight than adults (*see* "Causation of Rheumatism," chapter xvi.).

In drug action, salicylates were among the first things I used (Ed. v., p. 119), on account of the very great fluctuations they produce in the excretion of uric acid in the urine, and here again the granules were found to parallel the urine changes to an extent of which I had no expectation.

Thus on a day when I took 50 grs. of salicylate of soda and excreted 19·5 grs. of uric acid in the urine, the blood granules at 10.30 a.m. were 1 to 5. On the following day, no drugs being taken, the excretion of uric acid in the urine was only 12 grs., and the blood granules at the same hour in the morning were 1 to 36. On the following day, no drug being taken, uric acid had further fallen to 7·6 grs. in the day, and the granules at 10.30 a.m. were 1 to 75.

It, of course, is a very severe test of the granules to examine them at one moment of the 24 hours and compare them with the urine excretion of the whole 24 hours. Nevertheless, even apart from the large fluctuations caused by the salicylates, an examination of the blood about 10 a.m. in what is nearly the middle of the large alkaline-tide excretion of uric acid, will very often give a good index of a larger or smaller excretion of uric acid in the corresponding 24 hours.

On another occasion with upwards of 20 grs. of uric acid excreted in the urine as the result of taking salicylates, the granules in the morning were 1 to 4. On the following day with no drugs uric acid in the urine had fallen to 10·7 grs. and the granules were 1 to 34. On the following day uric acid had risen to 13·4 grs. and the granules were 1 to 10, both granules and excretion being here about the normal average.

Once again the blood was examined at 9 p.m., no drug being taken, and the granules were found to be 1 to 22, about the average for the time of day. Twenty grains of salicylate of soda were swallowed just after drawing the blood, and at 10.15 p.m. the blood granules had altered to 1 to 8, and at 11 p.m. were 1 to 6.

Similarly the granules can be increased in a few hours by a dose of alkali, or diminished to a corresponding extent by a dose of iron or mercury, or anything diminishing the excretion of uric acid in the urine.

In pathology, Thomas J., aged 10 years, on salicylates for erythema, had granules to red cells 1 to 1. The relation on the first day after leaving off the salicylates was 1 to 9.

Emily S., aged 19, salicylates beginning to relieve the pains of acute rheumatism, temperature 102°. Granules to red cells 1 to 2.

Rose O., aged 7, last day on salicylates for rheumatic fever 1—6
,, ,, first day on no drugs ... ... 1—11
Emily B., aged 21, sixth day of sub-acute rheumatism, no drugs, temperature 101° ... ... 1—18
,, ,, two days later pains relieved by salicylate, temperature normal... ... ... 1—4
,, ,, no drugs for three days... ... ... 1—12
William W., aged 12, on salicylates for acute rheumatism 1—3
,, ,, first day on no drugs ... ... 1—12

Several of these cases illustrate the large number of granules met with in children. Here the urine was not examined, and the blood simply taken in reference to the probable action of the drug.

In Bright's disease there is always a fairly marked excess of granules, thus:—

Julia A., aged 24, chronic Bright's disease, large pale kidney, blood granules 1 to 3.

Eliza S., aged 21, similar disease to last patient; granules 1—1 to 1—6, as the result of a large number of examinations.

I also examined the urine of Eliza S., and found a great excess of uric acid, on one occasion as much as 1 to 12 (*i.e.*, 1 of uric acid to 12 of urea), a relation unknown in physiology.

This is interesting because it has been suggested that kidney disease prevents the excretion of uric acid; yet in this patient, whose kidneys had probably not a single normal cell in any part, and in whose urine the microscope shows an immense number of casts with extensive fatty and degenerative changes, the excretion of uric acid is much larger than in physiology.

It is easy, however, to explain, for we have advanced disease with great debility, cardiac failure, general anasarca and sub-normal temperature; as a result, the alkalinity of the whole body is increased, the blood flooded with uric acid, and the most advanced degeneration of kidney structure will not, under these conditions, prevent its passing through the kidney into the urine.

In early and acute cases of Bright's disease, however, the excretion of uric acid is often, I believe, decidedly diminished, in spite of far less destruction of kidney structure than we had to deal with here. But in the more acute condition there may be some diminu-

tion of the alkalinity of the blood, and possibly still more marked diminution of the alkalinity of the kidney, and the uric acid is either not in solution in the blood or fails to pass the less alkaline kidney. In both cases it is a matter of solubility and not of minute structural integrity, and I have repeatedly seen kidneys which were found *post-mortem* practically destroyed, passing excess of uric acid as in the case of Eliza S.

Among cases which were probably granular kidney I may mention:—

John W., aged 63, granules		1—3
Caroline E., aged 43	,,	1—3
Abraham W., aged 60	,,	1—4
Joseph H., aged 38	,,	1—4

As to chronic gout, I have already mentioned one case, and another is that of Samuel H., aged 35, gout for fourteen years, and numerous tophi visible on the surface of his body and much general joint change, 1 to 2; and D. M. M., aged 52, chronic arthritis with depression, 1—6.

In fever one gets more or less marked diminution of granules, as—

William D., aged 20, 9th day of enteric fever, granules 1—30
Lucella T., aged 13 months, meningitis, temp. 101° ,, 1—14
(a relatively small number for a child)
Alice W., aged 10, 5th day of pneumonia, temp. 103° ,, 1—22

We see, then, that the granules are scanty in fever, numerous in gout, Bright's disease, and I may say also in diabetes in cases I have examined.

In physiology they precede all the well-marked fluctuations in the excretion of uric acid.

In drug action it is possible to make them vary in almost any direction and at any time.

These granules, I believe, are a perfectly reliable guide to the quantity of uric acid in the blood, for though it is not possible to get any chemical reaction as they exist in the blood, it is impossible to believe that any substance, so accurately following the excretion of uric acid in physiology and drug action, and corresponding so closely with what is known of uric acid in pathology, can be anything but uric acid or a form of xanthin capable of immediate conversion into it; for we know that xanthin is so converted in its passage through the body.

Other considerations make it probable that it is uric acid, and that this constantly exists in the blood in very similar colloidal

granules, but a trifle smaller and less visible than those produced by the action of chloride of ammonium.

But though I thus believe that these granules are a reliable index of the amount of uric acid in the blood, I do not often use them for that purpose, because, as will be seen in the chapter on the circulation, uric acid in the blood furnishes its own index by its effects on capillary circulation, and as these can be measured with considerable accuracy in less than one minute, it is only necessary to appeal to

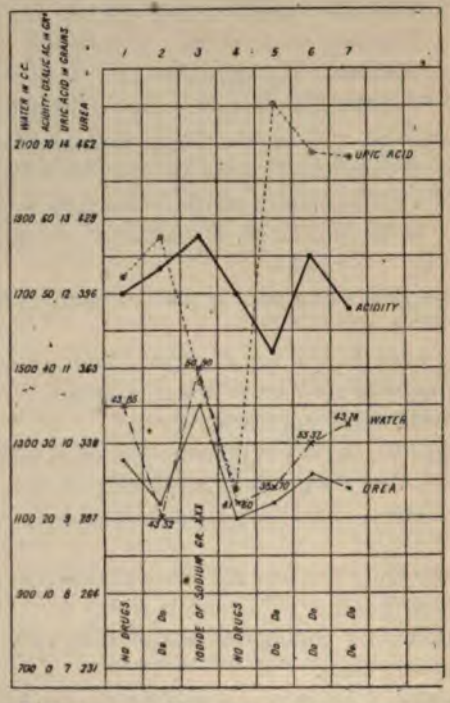

FIG. 22.—RETENTION OF URIC ACID PRODUCED BY AN IODIDE.

the granules when some special confirmation of the circulation evidence is required.

The granules, then, show that there is always some uric acid in the blood, more in the morning and less in the evening, corresponding with the excretion of uric acid in the urine, and that many of my previous results with the blood of venesection, and even with *post-mortem* blood, accord fairly well with our greater and more accurate knowledge.

Thus I found little in the blood in fever and inflammation, much in gout, uræmia and in death from pneumonia.

Indeed, as will appear later, I can control the condition of the blood by controlling the amount of uric acid passing through it, and the power gained in dealing with disease is commensurate with such knowledge.

Fig. 22 shows the effect of an iodide on the excretion of uric acid. On day 1 uric acid is high, and on day 2 it rises still further. On day 3 gr. x. of iodide of sodium are taken three times, and uric acid falls into close relation with urea; and on day 4, though no more of the iodide is taken, it falls further and remains close to the urea. On the remaining days of the figure no drugs are taken, but on day 5, the effect of the iodide ceasing, uric acid rises very high. This constitutes what I have spoken of as the rebound, and suggests that the low excretion of urate on days 3 and 4 was not due to destruction or elimination in other forms, but to retention in the body, the iodide rendering the blood a bad solvent of urates, with consequent retention in the liver, spleen, kidneys, and fibrous tissues; the effect of the iodide passing off they are again taken up by the blood from these organs and tissues and excreted in excess in the urine. A similar plus excretion follows the administration of all substances causing retention of uric acid. Substances, on the other hand, which cause a plus excretion of uric acid, as alkalies, salicylates, &c., are followed by a great fall in urate excretion the day after disuse (see figs. 7 and 8).

On days 6 and 7 in this figure uric acid remains high and a long way above urea.

Note also that the usual relation of uric acid to acidity is broken, for urate falls and remains low on the fourth day, though acidity has fallen decidedly. On the fifth, however, the effect of the iodide ceases, and the fall of acidity allows a plus excretion of urate; on the sixth acidity rises and urate falls somewhat, so that it has regained its normal relation to acidity.

Observe how the excretion of water rises to 1,500 cc. on the third day when the urate falls close to urea. On day 2 uric acid exceeds the relation to urea of 1—33 by nearly 3½ grs. (that is to say, on this day about 3½ grs. of uric acid passed through the blood), the capillaries of the kidney and of the whole body were obstructed by the urate, hence the urinary water was scanty, only 1,100 cc. On day 3 the iodide produces its well-known diuresis, which diuresis, like that of many other drugs causing retention of uric acid, is due to its clearing uric acid out of the blood. On day 3 uric acid was

above urea by only $\frac{1}{4}$ of a gr., and so only $\frac{1}{4}$ gr. passed through the blood, therefore the capillaries and the circulation through the kidneys were free, and the urinary water ran up to 1,500 cc.

In a paper on "The Iodides and their Effects on Arterial Tension and the Excretion of Urates" (*Transactions of the Royal Medical and Chirurgical Society*, vol. lxxvi., p. 113), I have pointed out that the relaxation of arterioles and diuresis which the iodides produce are contemporaneous with diminished excretion of uric acid in the urine, and that a large number of drugs and disease processes similarly diminishing the excretion of uric acid and clearing it out of

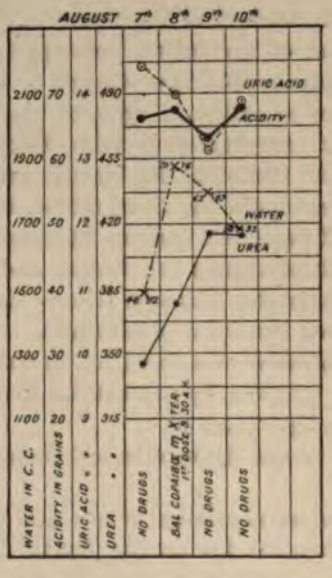

FIG. 23.—EFFECTS OF BALSAM OF COPAIBA ON THE EXCRETION OF URIC ACID AND WATER.

the blood, produce also a relaxation of arterioles, or, as I should now prefer to say, a freeing of capillaries, and a diuresis; and I assert that arterial tension is influenced, not by the drugs, but by their effects on the solubility of uric acid and the amount present in the blood.

Copaiba is another diuresis-causing drug, and fig. 23 demonstrates that (as with iodides) the increased excretion of water is contemporaneous with a fall in the excretion of uric acid. We are, therefore, to consider whether this action be not due to effects on the solubility and excretion of uric acid.

Here we see that on August 7 uric acid exceeded the relation to urea of 1 to 35 by nearly 4¾ grs., that is to say 4¾ grs. passed through the blood. The urine was rather scanty in the day hours, but this was balanced by an excretion of exactly double the amount at night. On the 8th, on which the copaiba was taken, uric acid fell and urea rose, so that only 3¼ grs. traversed the blood, and with this the water rises decidedly, being nearly twice as much in the day hours as on the 7th.

On the 9th, uric acid falls still further, and urea continues to rise, so that only 1¼ grs. of uric acid pass through the blood, and with this urinary water remains high, but the hourly excretion at night is again larger than in the day hours.

On the 10th urea is stationary, while uric acid rises so that 2 grs. pass through the blood, while the water falls and the hourly excretion at night nearly doubles that of the day.

Therefore on the 8th and 9th urinary water is high, and this corresponds with a well-marked fall in the quantity of uric acid then passing through the blood.

The diuresis produced by copaiba is therefore merely another illustration of the action of my law that the urinary water varies from hour to hour and day to day inversely as the height of the uric acid above urea, that is, inversely with the amount of uric acid passing through the blood (see descriptions of figs. 1, 2, and 3). We are less concerned with the manner in which copaiba interferes with the solubility and excretion of uric acid than with the fact of this action; but considering its composition one is struck with the large amount of acid (copaibic acid) it contains.

The rise of acidity on August 8 is small, especially as there is a pretty marked rise of urea; but something must have occurred to raise the acidity on the 8th, because it falls on the 9th in spite of a further and more marked rise of urea.

Several substances which produce similar effects (as tar, turpentine, cannabis indica, and guaiacum) contain very similar acids or acid resins; and I believe that a very large part of the physiological and therapeutic effects of these drugs can be explained by their action on the solubility and excretion of uric acid which controls the circulation. With reference to guaiacum I refer to my remarks in the debate on Sir A. Garrod's paper on this drug at the Royal Medical and Chirurgical Society (see Proceedings, 26th May, 1896, also *Lancet*, 1896, vol. i., p. 1494). In the above debate Dr. Norman Moore mentioned the interesting fact that in the 17th century guaiacum was considered the best remedy for tertiary

syphilis; it would certainly tend to clear the blood of uric acid, and free the capillary circulation just as do the present-day iodides.

We now come to uric acid, and a large group of substances almost chemically identical.

Uric acid and these related substances have important effects common to all, the chief of these being that they all hinder their own solubility in the blood; they not only do not remain in solution themselves, but prevent any other similar compounds otherwise present in the blood stream from doing the same.

Probably this effect is produced by an action like that of the nitrates, sulphates, &c., in taking alkali from the normal phosphates of the blood and converting them thus into acid phosphates non-solvent of uric acid.

The solvent powers of the blood being thus diminished, the blood stream is at once more or less cleared of uric acid, and the physiological and pathological effects of these substances depend entirely upon this action.

The substances which simultaneously clear themselves and their relatives out of the blood stream, pass, as we have reason to believe, into the parenchyma of the liver, spleen, kidneys, and many of the fibrous tissues; but when (perhaps introduced in food) a fresh supply of alkali enters the blood, the acid phosphates again become normal phosphates, and the solvent powers of the blood are restored.

The blood now acts on the uric acid previously driven into the tissues and organs, and keeps a certain quantity of it in solution until all is excreted by the kidney, or a fresh introduction of acids drives it again from the circulation into the tissues.

The urine is thus an absolute index of blood-condition, and it is obvious why the excretion of uric acid varies hourly and daily inversely with acidity of the urine.

Dr. J. Fawcett in *Guy's Hospital Reports* (1896, vol. lii., p. 40), objects to my statement that uric acid varies inversely as the acidity of the urine, and that the acidity of the urine is sometimes and in part due to uric acid, and thinks this last an unfair deduction.

I must explain that the inverse relation between excretions of uric acid and of acid in the urine is only strictly true in physiological conditions and where the daily introduction of uric acid is moderate and fairly regular; thus, if 10 grs. are taken to-day, 15 to-morrow, and 5 next day, there will be large variations in acidity and in excretion, and they will not always vary in the rule.

Again, if we consider that the excretion of uric acid in the urine is the resultant of two factors:—(1) The amount available; and (2)

the solvent power of the blood; we see at once that as the acidity of the urine varies for the most part with only one of these factors (*i.e.*, the alkalinity of the blood and its solvent power for uric acid), unless the other factor (the amount available or the introduction) is kept fairly constant, there will be exceptions.

Thus I increase my excretion of uric acid by taking an alkali, but if I also swallow some extra uric acid I obtain a still larger excretion than by taking the alkali alone.

My own physiological results were obtained on a practically constant diet, with a fairly constant and very small daily introduction of uric acid, therefore the amount available varied but little; yet the results are occasionally disturbed by introduction, especially in the curves obtained before I knew all I have since learned about the means of introduction.

In pathology the same rule obtains, but there are exceptions, such as gout and rheumatism, when the uric acid has, so to speak, an additional outlet, being taken up and deposited in the fibrous tissues already the seat of chronic irritation.

Here uric acid in solution is likely to be attracted to the urates already deposited (as uric acid on a filter attracts all the uric acid out of the urine poured over it), and therefore in gout it is not supplied to or excreted by the kidneys in such quantity as any given fall in the acidity of the urine might promise.

Hence the alternation of gout with melancholia, and of migraine with rheumatism; when urates are retained in the fibrous tissues and joints the blood contains relatively little, and high blood pressure and its effects are absent.

During the gouty condition the tophus in the big toe is daily increased by all the uric acid brought to it in the blood; but the rest of the blood is comparatively deprived of uric acid, and, the excretion from the kidneys being less than the acidity of the urine suggests, there is no high blood pressure nor melancholia.

Again, clinically, it is usual to hear a patient say that she suffered much from rheumatism a year or so ago, but that lately this has improved, while the headaches are worse. In other words, an increase of dyspepsia and debility, or other cause of a rise in the alkalinity of the blood, has reversed the above process, and urates are now taken up from the fibrous tissues rather than deposited.

We can now understand why Dr. Fawcett could not imitate my physiological results with alkalies in cases of gout; and matters were further complicated by foods (eggs, fish, tea, and occasionally full diet), which, varying daily, introduced disregarded amounts of xanthin.

With salicylate of soda, however, he secured results much more nearly resembling mine, for the salicylate at once brought the uric acid out of the gouty joints and fibrous tissues, and brought it in a steady stream to the kidneys for excretion (see action of salicylates, chap. ii.).

I may mention here that he did not observe that colchicum lowered the acidity of the urine; I notice, however, that he used the vinum, and in rather small doses; and sherry, as we shall see in fig. 63, distinctly raises the acidity of the urine, and would therefore tend to counteract the colchicum. In my experiments I used tr. colch. sem., the alcohol in which would at least not counteract the effects of colchicum on acidity of the urine.

Dr. Fawcett also thought he saw some exceptions to my rule as to the inverse relation between water and uric acid in excretion, but I doubt whether he had read carefully my remarks with reference to fig. 3; and in any case, with the very complex excretions he would get when dealing at once with pathology, drug action, and varying food and introduction of urate, I should not expect the rule to come out clearly.

But to return to uric acid and the xanthins: the primary effect of taking any one is to clear the blood of uric acid, and all other immediate effects are the results of the circulatory changes thus produced; the secondary effect is to flood the blood with uric acid, and this flooding accounts for the later effects. Fig. 24 shows both these series very well.

I now mention the chief substances in this group, with their chemical composition, and then describe in detail the physiological effects of a few of the most important.

Uric acid = $C_5H_4N_4O_3$.
Xanthin = $C_5H_4N_4O_2$.
Hypoxanthin = $C_5H_4N_4O$.
Purin = $C_5H_4N_4$.
Guanin = $C_5H_5N_5O$.
Kreatin = $C_4H_9N_3O_2$.
Kreatinin = $C_4H_7N_3O$.
Glycocoll = $C_2H_5N_2O$.
Thein or Caffein = $C_8H_{10}N_4O_2$.
Theobromin = $C_7H_8N_4O_2$.
Other vegetable alkaloids of similar composition.
Ptomaines.

I shall point out that as regards physiology and pathology it makes no difference whether a grain of uric acid, xanthin, hypo-

xanthin, thein, caffein, or theobromin is swallowed; all alike produce primarily clearance of uric acid from the blood, with free capillaries and general stimulation of metabolism and nutrition; all alike have a secondary action or rebound when the uric acid returns into solution in the blood, with obstructed capillaries and general depression of nutrition and metabolism.

What we know of several other vegetable alkaloids and their physiological effects points strongly to their acting in the same way,

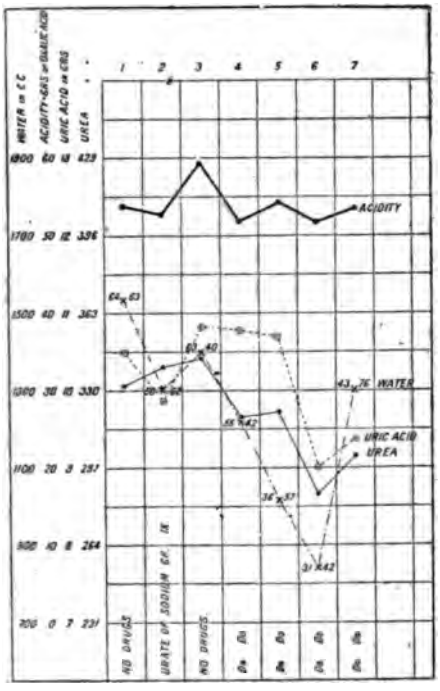

FIG. 24.—EFFECT ON THE EXCRETION OF URIC ACID OF SWALLOWING URATE OF SODIUM.

and our knowledge of ptomaines makes the possibility that such part of their action as resembles that of the above substances may be produced in exactly the same way worth consideration.

Guanin is a very similar substance, and glycocoll I have previously spoken of as uniting with benzoic acid to form hippuric acid, and with salicylic acid to form salicyluric acid (see salicyluric acid, p. 43); it also under certain conditions unites with ten parts of urea to form uric acid (see also p. 8).

All these substances thus form a natural group, which from my point of view is of enormous importance.

Now fig. 24 shows the effect of taking urate of sodium (grs. 9) by the mouth, and it apparently produces a rise in the excretion of uric acid in the first, second and third day after the dose. Its first effect is to clear the blood of uric acid, and with this clearance the excretion of uric acid falls below urea on day 2. The rise of acidity on

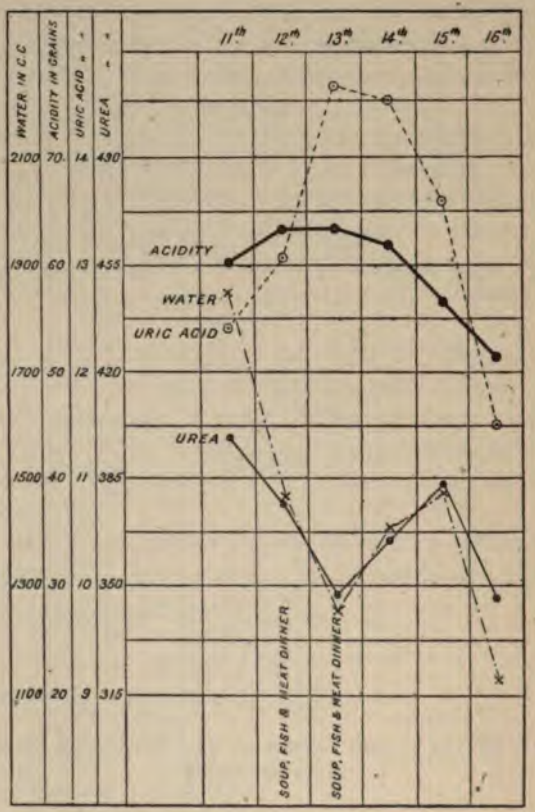

FIG. 25.—EFFECT ON THE EXCRETION OF URIC ACID OF SOUP, FISH AND MEAT.

day 3 is partly caused by the action of the urate on the phosphates of the blood before mentioned, and partly also due to the increased metabolism which follows the clearing of the blood, and this again accounts for the rise of urea on days 2 and 3. But the increased metabolism ends, urea falls and acidity with it, and the uric acid stored up on day 2 is re-solved in the blood and passed out in some

excess in the urine during the rest of the figure. Precisely the same thing occurs if uric acid is taken in place of a urate, but here again, on one of the following days, acidity falls, and uric acid rises and remains high for several days, more or less in proportion to the dose.

If, however, acidity is at a very high level, as in a person who eats much meat and drinks wine, uric acid or urates taken by the mouth may apparently produce no effect on the excretion of uric acid; for this excretion is dependent on solubility in the blood, and where conditions are unfavourable for this solubility it remains in the body instead of passing through the blood into the urine. In this figure it was the fall of acidity on day 4 that made the plus excretion of urate on this and the following day possible, but had no urate been introduced this fall in acidity might not have been followed by a rise in excretion.

If, on the other hand, the blood is prepared to hold uric acid in solution by supplying it with alkalies or salicylates beforehand, the uric acid or urates taken by the mouth pass almost at once through the blood into the urine, and by repeating and varying the dose, it is easy to show that excretion is proportional to the amount ingested. Thus in the *Journal of Physiology* (vol. xv., p. 167), to which I must refer for further figures and details, I have shown that, while a given dose of salicylate of soda produced in five days, under ordinary circumstances, an excretion of uric acid exceeding the relation to urea of 1 to 33 by 11¼ grs., a similar course of salicylate taken on other five days along with 12 grs. of uric acid, produced an excretion of 20¼ grs. above the relation to urea of 1—33.

I believe there is no reason to doubt that the extra 9 grs. excreted on the latter occasion came from the quantity ingested, and that if the experiment had been continued a day or two longer the whole of the 12 grs. would have been excreted.

Fig. 25 shows the effect on the excretion of uric acid of two dinners consisting of soup, fish and meat, taken on two consecutive days. On the 11th uric acid exceeded the relation to urea of 1—35 by about 1 gr.; on the 12th, the day of the first dinner, it exceeded it by 2¼ grs.; on the 13th, the day of the second dinner, by 4¾ grs.; on the 14th by 4 grs.; on the 15th by 2¾ grs.; and on the 16th, the last day of the figure, by 1½ grs.

It appears the effect of these two dinners was to introduce into the body and pass through the blood some 15 grs. of uric acid, or if we take off 1 gr. for each of the last five days in the figure on the supposition that as uric acid was above urea by 1 gr. on the 11th, it

might have exceeded urea by this amount on the following days even if no soup, fish or meat had been taken, we still get 10 grs. as the introduction of the two dinners, or 5 grs. for each.

In a paper in the *British Medical Journal*, 1894, vol. ii., on the "Direct Introduction of Uric Acid into the Body, its Bearing on the Prevention and Treatment of Disease," I have pointed out that, collating the quantities of various substances taken, and their uric acid or xanthins, a man may easily introduce nearly 2 grs. of uric acid with an ordinary dinner, and as we shall see in chapter xvii. that the percentages of uric acid from which this is calculated are probably decidedly under the truth, the introduction of 4-5 grs. is by no means extraordinary.

It appears from this figure that uric acid passed almost directly into the blood and urine, and there was no first stage of stimulation due to clearance of the blood. This illustrates a very important point, namely, that uric acid will produce one or other of two opposite effects, according as it is introduced with conditions favourable to its solubility in the blood, or the reverse.

Now in fig. 25 the conditions were distinctly favourable to solubility, because as I generally take neither meat nor wine the alkalinity of my blood rules high, and uric acid was already in some excess on the day before the first dinner. The first dinner, therefore, failed to stimulate and to overcome the depressing effect of the uric acid already in the blood, it failed, therefore, to raise either urea or acidity, and the uric acid it introduced passed almost at once into the blood and added its depressing effects on circulation, nutrition and metabolism to those of the uric acid previously there.

On the 13th almost the same thing occurred; there was again a failure of stimulation and a further fall of urea, and again the uric acid introduced passed almost at once into the blood and added to the general depression. The rise of acidity in this figure is slight, and was probably due to the rise of urinary acidity which excess of uric acid produces (see p. 40 and also chapter vii.), rather than to any real fall in alkalinity of the blood. But those who eat meat two or three times a day must not expect to introduce uric acid into their blood in the direct manner shown in the figure; with higher acidity (which they are certain to have so long as they keep well), the uric acid introduced will pass much more slowly into solution and be more gradually excreted; a dinner of this kind will act as a stimulant, they will feel better and stronger and happier for it. So long as they keep well, they have the best of it, and can point to very good results; it is true they are continually introducing considerable

quantities of uric acid, which may produce now and again more or less decided reminders of their presence in the shape of gout or rheumatism; but so long as the blood is kept moderately clear of uric acid by continued stimulation, there is no great harm done, and they may suffer neither from gout nor high blood pressure.

Unfortunately, however, as old age comes on, nutrition begins to fail, and further stimulation becomes more difficult; alcohol, morphine, and cocaine are perhaps called in one after another to help to

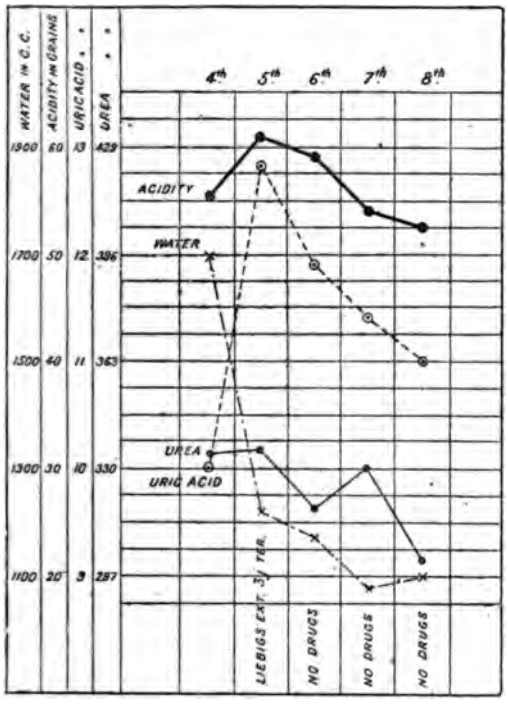

FIG. 26.—EFFECT ON THE EXCRETION OF URIC ACID OF LEIBIG'S EXTRACT OF MEAT.

keep the fires going brightly; at first they succeed; later, even in large doses, they fail, and then comes the disaster.

Urea and acidity fall down for the last time, and with this the long-pent-up store of urates breaks its dams and rushes into the circulation with an overwhelming flood. Circulation, nutrition, and function are soon rendered nearly impossible, and the physiological wreck has a chance of destruction by some of the terrible effects of severe collæmia, as we shall see in the following chapters. If it

escapes the rocks of cerebral hæmorrhage, it may drift through some years of the discomfort and misery of high blood pressure and chronic Bright's disease, to end in uræmia on the one hand or heart failure on the other. Long before this stage has been reached it will be obvious to onlookers that the meat-eater has got far the worst of the argument, and will pay a terrible price for his stimulants. Figs. 25 and 26 show what his meat does for him, and how it does it.

In following chapters it will be seen how uric acid blocks the capillaries, overworks the heart, prevents circulation, nutrition and

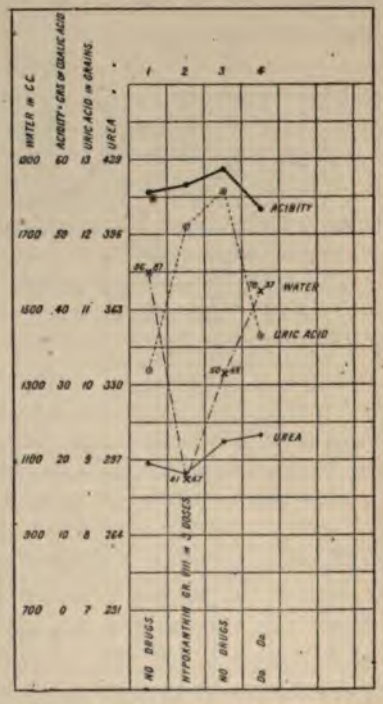

FIG. 27.—EFFECT ON THE EXCRETION OF URIC ACID OF SWALLOWING HYPOXANTHIN.

combustion, and produces anæmia, and how the effect of such meals as those recorded in fig. 25 is patent to anyone who can estimate the quality of the blood, its rate of circulation through the capillaries, or the effect of the capillary circulation on the blood pressure.

Fig. 26 shows in the same way as the previous figures the effects of meat extracts. On the 4th uric acid is below urea, urinary water is consequently high, and acidity stands about 55 grs.; on the 5th

3 drachms of Liebig's Extract are taken in the course of the day, and the effect is that urea remains steady, uric acid rises quickly and decidedly, and water comes down equally decidedly, while acidity rises a little above 60 grs.

Here, just as in fig. 25, the rise of acidity was probably due to the increased quantity of uric acid in the urine, and does not show diminished alkalinity of the blood, else the uric acid would not have been so freely excreted.

The rest of the figure indicates that uric acid falls, there being no further introduction, that acidity falls more or less in parallel,

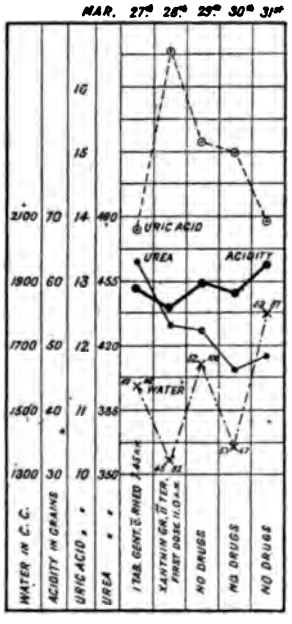

FIG. 28.—EFFECT ON THE EXCRETION OF URIC ACID OF SWALLOWING XANTHIN.

and urea falls also, partly, no doubt, owing to the diminished metabolism which excess of uric acid in the blood produces (see chapter viii.). Last, but not least, the water falls and remains low while uric acid is high, thus again proving obstruction of the capillaries of the kidney by excess of uric acid in the blood.

Will anyone, looking at these figures, tell me that I cannot control hourly and daily the excretion of water from the kidney, or the

circulation, function and nutrition of every organ and tissue of the body?

I shall demonstrate that what controls the flow of water from the kidney controls also its exhalation from the lungs, and also digestion and all digestive secretions.

Fig. 27 shows the effect of 8 grs. of hypoxanthin taken on day 2. It appears to increase very markedly the excretion of uric acid, which rises on days 2 and 3 in spite of a slight rise of acidity, and falls on day 4 in spite of a fall of acidity. Note also the inverse relation of

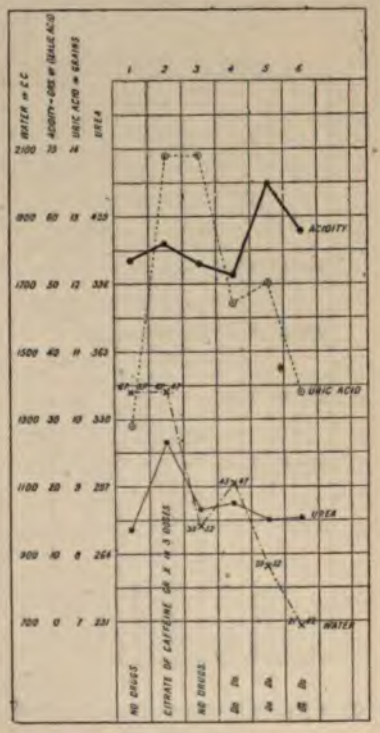

FIG. 29.—EFFECT ON THE EXCRETION OF URIC ACID OF SWALLOWING. CITRATE OF CAFFEIN.

the urinary water, which falls on days 2 and 3 with high uric acid, and rises again on day 4 as uric acid drops.

My remarks about the previous figures apply almost verbally here; the hypoxanthin does not appear to increase urea, and the small rise of acidity is probably due to excess of uric acid in the urine, and not to any change in the reaction of the blood.

It thus appears probable that metabolism disregards the slight chemical differences between members of the xanthin group, and passes the greater part of them through the blood and into the urine as uric acid.* And one important consideration obtrudes itself (though I must return to it later), namely, that if members of the xanthin group must practically be reckoned as uric acid, estimation of the uric acid present in any food gives an imperfect record of the amount it may introduce; for the xanthin and hypoxanthin are con-

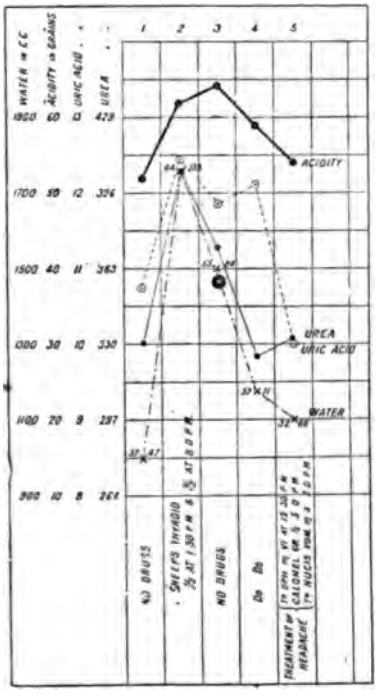

FIG. 30.—EFFECT ON THE EXCRETION OF URIC ACID OF SWALLOWING A SHEEP'S THYROID.

siderably underestimated. My table of the amount of uric acid found in various food substances must therefore be taken only as showing a part of what these may introduce, and important substances should be put to the more valuable physiological test of taking known quantities by the mouth, and estimating the increased

* As to the chemistry of this group see Lea, "Chemical Basis of the Animal Body," p. 182.

excretion of uric acid, as in the figures now described (see chapters i. and xvii.).

With regard to xanthin, Bunge says (in "Physiological and Pathological Chemistry," Wooldridge's Translation, 1890, p. 348), "xanthin occurs in too large quantity in the tissues and too small quantity in the urine to be eliminated unchanged," and fig. 28 shows that it is changed into uric acid.

Acidity being below 60 grs. a day, and the conditions favourable to the solubility of uric acid in the blood, it is nearly half a grain above urea on the 27th. On the 28th 6 grs. of xanthin are taken and uric acid rises sharply to about 4 grs. above urea, falling rapidly on the 29th, and more gradually on the following days. Urea falls from beginning to end of the figure very much as it does in fig. 26, and probably for the same reasons.

Fig. 29 shows the effect of a dose of 10 grs. of citrate of caffein taken on day 2, namely, a marked and immediate rise in excretion of uric acid, which remains high above urea on subsequent days of the figure.

On day 1 uric acid exceeds urea by about 1½ grs.; on day 2 by more than 4 grs.; on day 3 by more than 5; on day 4 by 3 grs., and so on.

Here then is another member of the xanthin group (for caffein is, chemically, trimethyl xanthin—Lea, prev. ref., p. 175), which taken by the mouth markedly increases excretion of uric acid, and the amount passing through the blood. This result is, I believe, constant, for I am able, by administering caffein, to produce pathological changes in the blood similar to those produced by uric acid taken in other forms.

The important corollary is that all vegetable alkaloids, which (like caffein) are chemically ureids or xanthins, are possible introducers of the elements of uric acid. I have already mentioned this in chapter ii. in alluding to the effect of quinine and strychnia.

Fig. 30 shows the effect of eating a sheep's thyroid gland, which also apparently produces on the second and third days some plus excretion of uric acid.

The first effect was a marked diuresis; the first dose of the gland was taken at 1.30 p.m., and did not greatly affect the urine of the day, which was 44 cc. per hour, but in the night it ran up to 138 cc. per hour.

Note that with this diuresis there was a rise of acidity and urea, and that uric acid barely exceeded urea, in other words, there was no uric acid passing through the blood.

Here is noticeable the primary stimulating effect; the secondary depressing effect was evident on day 4, and would have been more so on day 5, but for the necessary drugs which made my work possible.

Remember also, that acids, mercury, iodides, iron, lead, and a host of other drugs which retain uric acid, will produce a similar rise of urea and a diuresis.

The sequence in the case of this figure was probably thus: the thyroid gland introduced certain nitrogenous substances and acids or acid salts; these produced a rise of urea and acidity; this latter cleared the blood of uric acid and freed the capillaries. On this latter supervened a quickening of metabolism, and further rise of urea and acidity, and the clearing of the kidney capillaries permitted a profuse diuresis because the water had been scanty on day 1, and fluid had been accumulating.

On day 3 uric acid exceeded urea by ½ gr., and on day 4 by more than 4 grs., and doubtless would have exceeded it on day 5, but on the morning of this day there was considerable headache, and drugs which brought down the uric acid were necessary to cure it.

Note the large excretion of water on day 2 when uric acid was close to urea and none passed through the blood, and its steady fall on subsequent days when uric acid rose. Note also the scanty water in the day hours of day 5, when there was headache, and, no doubt, excess of uric acid in the blood, though the minus excretion produced by the drugs brought down the level for the whole twenty-four hours; but here the water indicates in which hours uric acid was scanty or profuse. In a paper in the *British Medical Journal* (1897, vol. i., p. 196) it is stated that the most active constituent of thyroid gland is a compound of iodine (iodo-thyrin or thyro-iodin) contained in the thyroid material, and this is most interesting, as I have mentioned the similar action of the iodides. If this is so the action of thyroid gland may be retention of uric acid, as shown in day 2 of fig. 30, followed by a rebound and plus excretion on days 3, 4 and 5, thus exactly resembling the action of this group of drugs. But I have little doubt that the direct increase of excretion on days 3, 4, and 5 was partly due to the nitrogenous extractives in which these glands abound (see Professor Foster's "Text-book of Physiology," ed. v., p. 762). In patients treated with these or their extracts, strong symptomatic evidence of the passage of excess of uric acid through the blood appears exactly as when uric acid is taken in other forms (see chap. xii.); and, in my experience, after long administration of thyroid, patients often suffer from depression of mind and body, these being, no doubt, contemporaneous with the

passage through the blood of some excess of uric acid thus introduced, but partly due also to a rebound from the action of the iodine compound. The administration of thyroid extract also affects the composition of the blood and precipitates attacks of angina or epilepsy, just as in fig. 30 it produced uric acid headache (migraine); and it acts in these cases to a considerable extent in the same way as uric acid or any member of the xanthin group. For a case in which apathy followed the taking of thyro-iodin, see *British Medical Journal*, 1900, vol. ii., p. 582.

Others have noted a large excretion of uric acid in the urine during thyroid treatment, and have seen some tendency to syncope as a result,* which bears on what I shall say presently in chapter viii. Mordhorst also refers, in his paper in *Zeitsch. für Klin. Med.* (to be mentioned in chapter v.), to the fact that eating calf's thymus greatly increases excretion of uric acid in the gouty and in the healthy; thymus being very similar both to the thyroid and to the spleen as regards its extractives.

Dr. W. J. S. Jerome has also found increased excretion of uric acid as the result of thymus feeding, and concludes that at least some part of the daily output of uric acid is due to the alloxur-holding bodies (*i.e.*, xanthins) in the food (*Journal of Physiology*, vol. xxii., p. 146).

The same observer (same Journal, vol. xxv., p. 98) found a distinct increase in the output of uric acid after use of Liebig's Extract, thus confirming my results.

He considers Minkowskie has conclusively established that one at least of the alloxur bases (viz., Hypoxanthin) yields uric acid in dogs and men, which again confirms my results.

He states that nuclein from spleen and yeast increases uric acid; but I observe that both spleen and yeast contain xanthin (as regards the latter, see Watt's "Dictionary of Chemistry," 1892, Art. Xanthin).

Dr. Jerome quotes from Kossell the quantity of alloxur bases found in fresh beef; of which, calculated as uric acid, the percentage is ·0841, or about 5·7 grs. to the pound, while the largest quantity I have found in beef is about 7·0 grs. per pound (see chap. xvii.).

A point of interest here is mentioned in a review of the fourth edition of this book in the *Edinburgh Medical Journal*, August, 1898, p. 173, namely, that "milk and cheese contain much nuclein."

This being so it must be clear that nuclein is not a source of uric

* *Lancet*, 1896, vol. i., p. 1446.

acid, for I can take daily for years as much milk and cheese as will produce from 300 to 400 grs. of urea without excess of uric acid or the troubles of circulation and nutrition it produces, while the same urea value in flesh, fish, or egg produces these troubles in a few days, with a great increase in the excretion of uric acid.

Again, Messrs. Hopkins and Hope point out (*Journal of Physiology*, vol. xxiii., p. 283) that thymus extract freed from nuclein still increases excretion of uric acid: probably it was not also freed from the alloxur bases. Now milk and cheese contain much nuclein, but being free from alloxur bases do not increase this excretion (see also my remarks in the *Journal of Physiology*, vol. xxiv., p. 156).

The conclusion seems obvious that nuclein itself does not give rise to uric acid when ingested, while the xanthin associated with it in certain tissues does so.

Giajinis (as mentioned in the Epitome of the *British Medical Journal*, September 10, 1898) found that liver increased the uric acid more than an equal quantity of muscle tissue, which is what should be expected, because it contains considerably more uric acid or xanthin.

Several of the drugs whose effects I have attributed to their action on uric acid, are believed to act directly upon heart or vessels, or both, or to influence certain centres in the brain and cord.

Much of this is admittedly hypothesis, and must not be taken as fact.

I do not wish to deny their action on the vessels and nerve centres. My facts do not carry me so far, and I shall not exceed them by a fraction.

This, however, need not prevent logical deduction from observation.

To state, for instance, that the mental stimulation and well-being produced by small doses of opium is caused by direct action on the vessels and nerve tissues, is to present two causes where one suffices.

Opium clears the blood of uric acid, thus freeing the capillaries all over the body, and altering the circulation from head to foot.

The altered cerebral function is either due to altered circulation or it is not. If not, why does every one of the long list of drugs mentioned above as clearing the blood of uric acid, and lowering blood pressure, produce like effects on the cerebral function?

Do such drugs as copper, zinc, mercury, silver, lithia, acids and opium all affect the vessels or the nerve substance alike, or is their

action due to that factor which is alone common to them all—an effect on the solubility of uric acid in the blood, and so on the circulation?

When any of these drugs produce results differing from those produced by all the drugs possessing a common action on uric acid, some other explanation of their action must be found, but not till then.

I have shown that if opium is given when there is diarrhœa, or the alkalinity of the blood is very high, it will with difficulty reduce this alkalinity and affect the solubility of uric acid, and in these circumstances its usual effects upon cerebral function, as also upon muscle function, and the consequent fatigue, will be more or less completely absent. When opium has thus failed, a drug such as mercury, which clears the blood of uric acid by the direct formation of an insoluble compound with it, and is therefore independent of alkalinity and acidity, will succeed (see Fatigue, chap. viii.).

All these drugs and many more that clear the blood of uric acid and alter the whole circulation, affect not the cerebral function merely, but the action of every gland and tissue, thus increasing the formation and excretion of urea; but should their action on uric acid be prevented, the other effects fail to appear.

Thus salicylates cause diuresis, but not while uric acid is high, only during its decrease on the second or third day of their action; whilst it is high urinary water is scanty. But drugs which clear the blood of uric acid at once, produce diuresis in a few hours.

I am unable to suppose that any of these drugs produce diuresis by acting on the renal epithelium.

If it be said that they affect the renal vessels in common with all the other vessels, and thus only, I do not object.

Here is a large group (only a few of which I have discussed), diminishing excretion of uric acid in the urine by clearing it from the blood. To state that these substances produce diuresis by acting on the renal epithelium, mental brilliancy and well-being by action on the nerve centres, increased flow of saliva by action on the salivary epithelium, and of other excretions by action on the cells of stomach, intestines, liver and skin, with increase of urea by action on muscle fibre, and of expired water by action on the pulmonary epithelium—to present this complication, and to ignore the fact that all these substances free the capillaries, lower blood pressure, and so affect the circulation throughout the body and its tissues, is to multiply perplexity where nature offers a simple issue.

In the case of any substance with power of diminishing excretion of uric acid, and as a result (for it occurs constantly in

physiology) increasing excretion of water, it can be shown that it increases the urine, the sweat, saliva, and all digestive secretions and functions; but it increases the water given off from the lungs, raises the temperature of the skin and extremities, and increases the formation of urea, thus dominating the phenomena of fatigue; and all this concurs with a general freeing of capillaries and fall of blood pressure, and everything that produces these two last effects will also produce the others.

Uric acid itself is singly a splendid diuretic, but if administered with solvents such as salicylates or alkalies, it renders the urinary water more scanty, for its action is then to block the renal capillaries rather than to free them. Thus the action of this group is due not directly to injection, but to effect on the amount of uric acid in the blood and so upon the circulation in the renal and other capillaries. Injecting uric acid into the blood clears it of uric acid and so produces diuresis. It is therefore impossible to raise the blood pressure by injecting uric acid into the circulation.

A note on this subject occurring in the Epitome (of the *British Medical Journal*, October, 1903, page 56) on Theocin has interested me, because reference is made to the general diuretic effect of xanthin derivatives. All these derivatives clear the blood of uric acid, and everything with this action frees the renal capillaries and increases urinary water.

In fig. 23 we see the rise of water and also of urea, and similarly in fig. 22 this double rise occurs, when uric acid is brought down by iodides; a similar rise of water, following the clearance of the blood of uric acid and the rapid improvement of the blood decimal, is seen in a case where iodide of mercury was taken for chlorosis (fig. 57).

We shall see that iodide of mercury is perhaps our most powerful drug, and the most efficacious in clearing the blood of uric acid, and counteracting most of its pathological effects.

But even this drug may fail ignominiously, if it causes salivation and gastro-intestinal irritation and diarrhœa, for these invariably depress urea and acidity, and increase the alkalinity of the blood. They will also diminish the absorption of the iodide, and the collæmia and its effects will therefore continue. The stomach and intestines must be in working order before the excretion of uric acid can be diminished with drugs.

The primary stimulant action of the uric acid group being thus defined, and it being proved that this is due to their temporary interference with the solubility of uric acid in the blood, we can

explain the primary stimulating effects of tea, coffee, cocoa, guarana, beef-tea, meat extracts, soups and thyroid extract, also the use of such things as pigeon's dung in ancient prescriptions, and child's urine as a stimulant by some nations at the present day.

It is an interesting point that these stimulating effects are in all cases due to the same chemical substance, and are produced in the same way, and that depression requiring further stimulant for its removal is the invariable consequence.

I was informed by the late Mr. H. B. Meakin, formerly house surgeon and house physician at the Metropolitan Hospital, that in Morocco the popular remedy for severe fright in a child is a drink of urine, preferably that of a virgin. If by a virgin is meant a girl recently arrived at puberty, her urine would probably then contain more uric acid than at any other period (see fig. 59).

Dr. Rushton Parker has obliged me with a reference to a paper by Dr. R. Neale in "Food and Sanitation," June, 1894, p. 195, where he says, "In South America the urine of little boys is spoken of highly as a stimulant in malignant small-pox.

"Among the Chinese and Malays of Batavia, urine is very freely used. One of the worst cases of epistaxis ceased after a pint of fresh urine was drunk, although it had for 36 hours or more resisted every form of European medicine. This was by no means an unusual result of the use of urine, as I was told by many of the natives. As a stimulant and general pick-up I have often seen a glass of child's or young girl's urine tossed off with great gusto and apparent benefit. Dr. Hastings' report of the value of the excreta of reptiles in 1862, in the treatment of phthisis, will also be fresh in the recollection of the older members of the profession."

In epistaxis the urine had doubtless the same effect as iodide of mercury, of the value of which in other forms of hæmorrhage I shall speak presently, *i.e.*, it cleared the blood of uric acid, and lowered the blood pressure. Reptiles' excreta in phthisis act in the same way as meat diet and other things to be dealt with in chapter ix.

Fright is a powerful depressant, producing collæmia and disturbing digestion and metabolism (hence its common connection with the onset of chorea, see chapter xvi.), and a draught of urine or dose of uric acid would, as some of the preceding figures show, clear the blood of uric acid and put an end to its depressing effects. Almost any of the above-mentioned stimulants would do as well, but possibly in Morocco urine is more easy to obtain than the others.

Mr. G. S. Haynes cites a case known to him—that of a black-

smith of middle age suffering from aneurism of the aorta, with a history of severe recurrent sore throat, "which frequently went on to quinsy." He was advised by a friend to apply to a gipsy. She directed him "to make his own water and drink it."

The quantity of urine taken was two or three tumblers, and it was also used as a gargle. The benefit was marked, and the disease could always be thus checked at its onset. This is very interesting, for the relation of recurrent tonsillitis to fatigue in gouty and rheumatic subjects is well known. Fatigue is accompanied by collæmia, and the draught of urine would clear up the collæmia, just as do the iron, mercury, &c., in common use for this trouble. Hence, probably, the value of feeding up, beef-tea and meat extracts, &c., in such cases.

These figures (24 to 30), then, practically show:—that uric acid and many substances chemically related to it, as the xanthins, alkaloids and ptomaines, whether in food or as an addition to food, pass into the blood, and, when the conditions are favourable to their solubility, remain there until excreted in the urine; that they are not to any appreciable extent converted (as was supposed) into urea; that the rise of urea which they produce is secondary to the rise of acidity also produced by them; and that other acids, *e.g.*, sulphuric, introducing no nitrogen into the body produce a similar rise in the excretion of urea.

From these facts we may draw a few general conclusions.

(1) That the amount of uric acid in the blood of man (and probably of animals) is not a matter of chance, but is subject to certain definite rules. These, I believe, may be summarised thus. The amount of uric acid in the blood is proportional to its solvent power for uric acid and its salts. Increase of this power correlates increased urate in the blood, so long as the body can provide urate for solution. By influencing the solvent power of the blood we can influence within limits its contained amount of uric acid; we can also influence it indirectly by the amount of uric acid introduced in food.

(2) Excess of uric acid in the blood means contemporaneous excess of uric acid over urea in the urine; but, since the urine in the bladder may be a mixture of urines excreted under several different conditions of blood, too close a correspondence of the two fluids must not be expected.

This rule probably holds in physiology, but in pathology there is at least one well-marked exception, namely, nephritis; for here the alkalinity of the kidney is probably diminished by irritative pro-

cesses, so that there may be (and according to Profesor v. Jaksch there is) excess of uric acid in the blood, which yet may be unable to pass the kidney into the urine. Hence there may be in nephritis chronic retention of urates and chronic collæmia (with well-marked symptoms) without excess of urates in the urine.

Probably in the kidney acids at once induce retention of uric acid, and an instance perhaps occurs in the relatively large amount of uric acid in the kidneys of the dog to which I had administered hyposulphite of soda (p. 81), the small amounts in its blood and urine being results of this retention.

(3) The quantity of urate in the various organs and tissues seems to observe a certain order of proportion: thus, the liver and spleen have most, the kidneys decidedly less, and the muscles least; the quantity in the blood varies considerably, but it always contains less, often much less, than the liver or spleen.

The *post-mortem* blood quantities again bear fairly definite relations to certain diseases; in pneumonia cases there is almost sure to be a large quantity; in meningitis and others, where the temperature is high, and rising at death, there is very little, while in death from chronic wasting disease there will be much, especially with urate deposits in the joints.

Where the kidney contained so-called uric acid infarcts the temperature was high and rising at death, which was due to marasmus. The urate had been driven from the blood, and we should therefore expect little in it, while the infarcts in the kidney probably show us one of the places into which it was driven, there being, in fact, a gout of the kidney, possibly secondary to the irritation of previous collæmia.

It seems to me practically certain that, when uric acid is found in *post-mortem* blood in excess, it was in excess in the blood at the time of death, and was leaving it in excess in the urine, the excess in both fluids being due to the causes which determine excess during life.

I have shown that I can alter the amount of uric acid in the urine, and that I have good clinical reasons for believing that I simultaneously alter the amount in the blood; that when I increase the amount in the blood by giving an alkali, obstruction of the capillaries throughout the body follows, thus raising blood pressure, slowing the heart, and causing deficient circulation in numerous organs, the effect of which is visible in cold surface and extremities, mental depression or headache, and scanty urine with a relative excess of uric acid.

Reversing the process with an acid, I free all the capillaries, driving the uric acid from the blood into the liver, spleen, joints, &c., and if much of it is sent into the latter it generally renders its presence clinically evident by shooting and pricking pain, or severe irritation tending to distinct arthritis; the free capillaries allow a lowering of blood pressure and the heart quickens its pace, the surface and extremities become warm, the mind is clear and tranquil, the urine increases in volume, and indicates diminished uric acid.

But the varying amounts of uric acid in the urine, when thus produced, are merely alterations in excretion, and the quantity to be found in the blood at any time depends on its solvent power, the amount of uric acid introduced in the food, and previously stored in the liver, spleen, joints, and other tissues on which the solvent can act. When the alkalinity of the blood (*i.e.*, its solvent power for uric acid) is reduced it contains little or none; when its alkalinity is increased it may contain a very large quantity.

All fluctuations in excretion taken over a long period of time practically balance each other, giving a result near what I believe to represent the real formation of uric acid, viz., 1 of uric acid to 30 or 35 of urea.

Though the large excretion of uric acid in splenic leucocythæmia, for instance, may appear an excessive formation, it is probably merely the passage of large amounts of uric acid retained in the early febrile stages of the disease. In a case of this kind which I examined after death, I found in the blood ·06 per cent., a very large liver and spleen contained between them 100 grs. of it, there were urate calculi in one kidney and erosion in the great toe-joint, but no deposits of urates there (see "St. Bartholomew's Hospital *Post-mortem* Book," case of N. T., age 32, April 25, 1892). Here the urates were in process of solution and excretion, and some were deposited in the kidney on the way, while probably the liver and spleen contained much more uric acid earlier in the disease, since in these cases we know that there are often intercurrent pyrexial attacks during which the spleen enlarges (see *Lancet*, vol. i., 1892, p. 965), and when the store of urates in the liver, spleen and joints, and the body generally is increased. So that while I do not deny that a process of which I have no knowledge, viz., excessive formation of uric acid, may occur (in excess that is of the usual relation to urea), I believe all my results, as well as those of Professor v. Jaksch, can be explained by fluctuations in excretion, aided, as is generally the case, by more or less constant introduction, and further, that all the results produced by drugs favour this ex-

planation, but are inexplicable on any theory of excessive formation or deficient oxidation.

If, for instance, the plus excretion of uric acid under alkalies or salicylates (figs. 6 and 8) is due to plus formation, why does it, except under pathological conditions, not continue longer than two or three days? Even in pathological conditions it does not last long, for in the case of splenic leucocythæmia, of which I give notes in chapter xii., a course of salicylate of soda sensibly diminished excretion; whereas at the first administration of the drug I got excretions of 1 of uric acid for 12 of urea, it lessened, as the drug was continued, to 1 to 24 or less; in other words, the stores of urate in the body were slowly reduced.

That the liver, spleen, and joints contain large amounts of uric acid, is in accord with Sir A. Garrod's theory and my explanation of my results; and in accordance with these the amount in all these organs and tissues can be altered at pleasure.

This explanation satisfactorily accounts for the well-known physiological fluctuations in the excretion of uric acid, and for the previously recorded relations of a series of diseases, as, for instance, the alternation of gouty arthritis (*i.e.*, retention of uric acid going on in the joints and its absence from the blood), with such diseases as headache, epilepsy, mental depression, and glycosuria, accompanied by excess of uric acid in the blood and urine. The arthritis corresponds with free capillaries and low tension pulse due to absence of uric acid from the blood, and the latter diseases correspond with obstructed capillaries and high tension pulse due to excess of uric acid in the blood.

In all these cases the excretion of uric acid in the urine corresponds with the amount in the blood, and these facts have been recorded by observers without knowledge of their relation to uric acid.

It is, I think, impossible to explain these facts either on the theory of excessive formation or on that of deficient oxidation, while Sir A. Garrod's dictum on lead-poisoning, "the blood becomes loaded with uric acid, not from its increased formation but from its imperfect excretion," serves, with the help of later knowledge about introduction, to explain the situation.

It is now, I hope, obvious that not only the physiological fluctuations in the excretion of urates and most of the pathological alterations are explicable, but that in accordance with my law of solubilities we can imitate Nature and demonstrate the effects of collæmia on the function, nutrition, and structure of the tissues of the human

body to any required extent; and where the urates already in the body are insufficient, we can increase them by ingestion in one form or another (see also chapter xii.).

Some of my fellow-workers believe that Horbaczewski has proved uric acid to be formed from the nuclein of cells, especially that of white blood cells.

Supposing for a moment that this is so, I point out that it affects in no way the facts I bring forward or the conclusions founded upon them.

For if it be true that the nuclein of certain cells is converted into uric acid, the rest of the cell may be simply converted into urea, and the relative formation of these two not be affected thereby. This would be in accord with the suggestion of Sir A. Garrod, that certain cells in the kidney form urea, and certain other cells, less in number, form uric acid.

Horbaczewski's observation that feeding on nuclein increases excretion of uric acid is probably correct, but this does not amount to proof that there is any new formation of uric acid; for is it quite certain that the nuclein or the spleen pulp from which it is obtained does not contain xanthin, hypoxanthin, &c., merely introduced into the body as the previous figures show to be possible, and is it not a fact that spleen pulp and nuclein contain phosphates, and that these phosphates may increase excretion of uric acid by acting as solvents (see fig. 7)? If this be so, the administration of nuclein after a course of salicylates would produce less increase in the excretion of uric acid than the same quantity of nuclein administered before it.

Dr. O. K. Williamson has an interesting article in the *Lancet*, vol. i., 1903, page 1580, on the relation between the excretion of uric acid and the breaking down of the white corpuscles, showing that the evidence is by no means all on one side as regards this relation.

His figures indicate that the rise in excretion of uric acid generally corresponds with a rise in excretion of phosphoric acid, but, if this phosphoric acid is excreted as phosphate of soda (a solvent of uric acid), the rise of uric acid may be due to this increase of solvent power in the blood, and is by no means a proof of a new formation. Nor did he always find definite evidence of the destruction of white cells to account for the rise.

It is surprising that he refers to this volume (though he gives no page reference) as showing that there is no retention of uric acid in cases of advanced pulmonary tuberculosis, which would depend, no doubt, upon the exact state of the disease. But with fever there is

sure to be some retention, and this is, I believe, the explanation of the well-known spes phthisica. It seems to me that the question at issue in Horbaczewski's observation is whether the excessive uric acid is the result of the increased destruction of leucocytes, and though this point cannot yet be determined, it may be of interest to remark that a similar increase in excretion of uric acid can be produced by administration of uric acid or xanthin proportional to that contained in the proteid food, and that the excretion of uric acid is proportionate to the amount of xanthin contained in such food. It has been remarked by Dr. Oliver that boiled meat (with some of the xanthin therefore extracted) has less effect on blood pressure than roasted meat. I see no proof whatever that the uric acid really comes from the destroyed leucocytes. I believe that it is either dissolved out by the increase of phosphate of soda or the uric acid itself, as suggested in chapter x., may cause the increased leucocytosis and the increased destruction of cells, both white and red.

There is no excessive uric acid output with proteid feeding, as is often so confidently asserted by those who probably never made an experimental investigation in their lives; for if they had made one they would have found that uric acid was only increased after certain proteids, namely, those which contain xanthin and similar substances.

You may feed milk and cheese to any extent, and you will never get a rise of the uric acid excretion above the relation to urea of 1 to 35, which is the relation of formation in the body.

But feed exactly the same amount of proteid from substances that contain xanthin and you will get a rise above that ratio, and this rise is due to introduction.

It is just as absurd to say that uric acid produces no symptoms; why then is the capillary reflux always slow in the morning and quick in the evening? Why does it always vary with the amount of uric acid in the blood? Why can it always be made to vary by administering or withholding uric acid?

Again we have the simple fact, of which there is now abundant evidence, that leaving out uric acid and the foods that contain it prevents and cures hundreds of "diseases," far more than I have even named in my writings.

Indeed, it must require several generations of correct living before we can see anything approaching its full effects.

But Horbaczewski's conclusions affect me little; if they prove true, we shall merely add nuclein to the list of substances which are

either potentially or *de facto* uric acid, or so closely related that human physiology makes short work of the small difference.

Whether uric acid is present in animal tissues as nuclein, as xanthin, hypoxanthin, or as urates visible to the naked eye, matters little, for the fact remains that when taken as food they produce disease by uric acid poisoning.

If it were true that uric acid is at once converted into urea, then Horbaczewski's conclusions would stand on stronger ground, for any increase of uric acid, he observes, must be due to new formation. My results, however, show that uric acid in foods is not converted into urea; it is absorbed unchanged into the blood, and passes gradually into the urine in quantity proportional to the amount introduced.

The answer research returns to my query as to the connection between the ingestion of animal tissues, their products, uric acid in other forms, and the causation of the uric acid headache (migraine), is that these substances not only introduce a considerable quantity of uric acid, but this introduction interferes with the solubility in the blood of uric acid previously formed or introduced; therefore there is a double tendency to form a store of uric acid in certain organs and tissues of the body.

It is known that it is possible to give large amounts of albumen in the form of white of egg, cheese, &c., without any great increase in the excretion of uric acid. If a similar quantity of albumen is given in meat, the increase is marked, and if in liver, spleen, and other glands, it is very large indeed.

The explanation is simple; the one set of foods contains uric acid ready formed, and the other does not; and the great conclusion is that the one is suitable for human food and the other unfit.

Swallowing uric acid as a dose produces a similar rise in excretion, and, when conditions affecting solubility in the blood are adjusted, the rise in excretion is rapid; this rapidity furnishing further proof that we have to do with excretion and not formation.

As the result of more or less natural changes in the alkalinity of the blood, the urates thus introduced and stored tend to pass into solution, and uric acid may then for a time be present in the blood in considerable excess; this excess of uric acid causing such circulatory changes as amply account for the headache.

Lastly, this headache can be prevented by stopping needless introduction of uric acid, and this without the reduction of urea below the physiological level of $3\frac{1}{2}$ grs. per lb. per day, if the required nitrogen be procured from foods free, or nearly so, from

uric acid or xanthin compounds. We should probably not be far wrong as regards this country if we attributed the migraine headache and most of its concomitant symptoms to poisoning by the flesh of animals, aided by thein and similar vegetable alkaloids, for the uric acid diathesis in causation is nothing but a myth.*

Were this the only result of my research, I should not regret my labours; but in the course of investigation it has become evident that many diseases own a causation practically identical with that of the uric acid headache, and further, that uric acid, in controlling the circulation, exercises a directing power over human physiology unimaginable before these facts could be, as they now can be, demonstrated.

* See article on "'The Uric Acid Diathesis,' Are we to continue to believe in it?"—*Edinburgh Medical Journal*, July, 1897.

CHAPTER IV.

Uric Acid and Metabolism.

At this point I propose to summarise what we have learned, and also the position which I shall take in succeeding chapters, leaving my readers to judge the evidence which has led to my conclusions. And I remind them that I am presenting no finished picture, but a preliminary communication on a progressive research, a subject which is still plastic in all directions, and where much remains to be learned.

Uric acid in the title of this book, and throughout the book itself, unless otherwise specified, is used as an inclusive term, comprehending uric acid and its salts.

We see, then, as the result of my researches that the uric acid daily excreted in the urine may come from three sources: (1) uric acid or urate formed from nitrogenous substances with a certain amount of urea, probably in the proportion of 1 of uric acid to 30 or 35 of urea. (2) Uric acid, urates, and members of the xanthin group, as caffein and other vegetable alkaloids, introduced with food. (3) Uric acid or urates stored in the body which pass into the blood when its alkalinity favours their solution.

When in the urine of 24 hours uric acid is present in the relation to urea of 1 to 35, we conclude that this uric acid was formed with urea of that day, and passed directly down the ureter into the urine, there being no uric acid furnished direct from the food or from the reserve in the body. If any was introduced in the food this did not remain in the blood, because conditions were unfavourable to its solubility, and for the same reason no uric acid was taken up from the stores in the body.

If, however, uric acid was excreted in the relation of 1—20 or 25 of urea, we conclude that the excess over formation (1—35) consists

of uric acid introduced with the food or taken up from the deposits in the body, or both.

Under these conditions it is comprehensible why all substances which form soluble compounds with uric acid, or increase its solubility in the blood, increase its excretion; and why all substances which form insoluble compounds with it, or diminish its solubility in the blood, diminish its excretion.

If, however, the excretion of uric acid is very low, having the relation to urea of 1—45 or 1—50, we must conclude that some of the uric acid formed on this day met with conditions in the kidney, the liver or other organs and tissues, unfavourable to its solubility, and was retained there instead of passed down the ureter; it being possible for the kidneys to contain an amount varying from a small percentage to a quantity plainly visible to the eye (see p. 78).

I regard the formation of uric acid in the body as practically constant in relation to urea; while excretion varies partly with conditions affecting its solubility in the blood and partly with quantities available for solution, *i.e.*, those introduced in the food, or previously retained.

I absolutely disbelieve in the formation of uric acid as a cause of disease; nor do I see any proof that the gouty man forms more than others in relation to urea. But the gouty man often indulges largely in animal flesh, and, as a result, forms more urea per pound of body weight than physiologists would allow, with some extra uric acid in normal proportion to urea, and also absorbs directly a considerable quantity of uric acid or xanthin compounds. I take, therefore, a hopeful view of these diseases, because errors of diet can be eliminated: whereas if there were an excessive formation of uric acid owing to a fault in the metabolism of the gouty this might be beyond remedy.

It is then in our power to control excretion of uric acid by regulating (1) the conditions affecting its solubility, (2) the quantities directly introduced in food, and (3) the quantity of nitrogen in the food, from which uric acid can be formed in the relation to urea of 1 to 35; and the fact that we can in this way regulate and control many disease processes, amounts to proof that the above deductions are not very far from the truth.

From the clinical history of the uric acid headache we learn that at the time of the attack, when there is an excess of uric acid in the blood and the urine, the pulse is generally slow, and of high tension.

It will appear that this is due to obstruction of the capillaries, of which there is abundant evidence in the concurrent cold skin and

extremities. Slight experiment will be conclusive that obstruction of the capillaries varies directly with the uric acid circulating in the blood, even if fig. 5 does not of itself suffice to prove it. And this obstruction of capillaries will produce two results: (1) rise of blood pressure in the heart and great vessels on the proximal side of the obstructed vessels—high arterial tension, or high blood pressure; and (2) deficient circulation and interchange between the blood and the tissues in, and on the distal side of, the obstructed vessels.

It follows from this that drugs and disease processes diminishing the excretion of uric acid and clearing it out of the blood will lower blood pressure and improve the circulation through all the organs and tissues.

Drugs have already been mentioned. The most important disease process with this effect is fever, which lessens the alkalinity of the blood, and thus prevents its holding much urate in solution.

Conversely, drugs and disease processes which increase the excretion of uric acid and bring it more plentifully through the blood raise blood pressure, and diminish or hinder the circulation through all the organs and tissues.

The most important disease processes with this effect are Bright's disease, post-febrile conditions, dyspepsia, splenic leucocythæmia, marasmus, and the cachexia of new growths, &c., for in conditions of low or failing nutrition there is commonly some increase of the alkalinity of the blood rendering it a more than usually good solvent of uric acid; and in post-febrile conditions not only is the blood a good solvent, but a large supply of uric acid is at hand, namely, that which was retained during the low alkalinity of the acute febrile period.

Now, other things being equal, freeing the capillaries of the kidneys means a free flow of urinary water, and their obstruction means scanty water; for this reason urine is scanty (30 cc. per hour) during the uric acid headache (migraine), and profuse (60—160 cc. per hour) during the precedent and following minus excretion of urates.

Not only is this true in pathology, but so constant is the relation of obstructed capillaries to uric acid, that in physiology also hourly and daily urinary water varies inversely as the excreted uric acid; or (more accurately), other things being equal, the more excretion of uric acid exceeds the relation to urea of 1 to 35 the more scanty will be the corresponding hourly or daily excretion of water, and *vice versâ*, because the uric acid excreted in excess of formation (1—35) passes through the blood on its way to the kidneys.

It follows that all drugs and disease processes diminishing uric acid excretion and clearing it out of the blood must increase the flow of urinary water, and hence I believe the *modus operandi* of the great majority of so-called diuretic drugs.

And drugs and disease processes producing or accompanied by an increased excretion of uric acid will also be accompanied by scanty excreton of urinary water; so that the hourly excretion of urinary water being known, the proportionate excretion of uric acid can be calculated with sufficient accuracy for many clinical purposes.

This relation between uric acid and water is visible in nearly every figure in this book, and during my years of experiment I have not met with any real exception to the rule, if one bears in mind that excretion of water depends partly on the freedom or obstruction of capillaries and partly on the supply of water available, since obviously no freedom of capillaries will cause diuresis when all fluids have been drained from the blood and tissues by vomiting, diarrhœa or perspiration; while conversely slight and imperfect freeing of capillaries may produce marked diuresis when there is excess of water in the blood and tissues (dropsy).

One to 33 is the relation of uric acid to urea in excretion, which I arrived at after a few months' work, and it forms the basis of all the older curves of excretion in the book. Further investigation seems to show that while the relative formation of uric acid to urea is about 1—35, as in the more recent curves, excretion varies greatly with the amount of urate (previously stored in the body) available for solution, and that daily introduced in food.

For the purpose of getting a synthetic view we may roughly classify uric acid diseases in two groups :—

A. The local or precipitation* group, due to the irritating presence of uric acid in a fibrous tissue either in solution or suspension (colloid form), as in gout.

Gout.

Rheumatism.

Morbus cordis (inflammatory).

Local inflammations of all fibrous tissues, some of which are to be found in the—

Brain and meninges.

Nose, pharynx, larynx, trachea, bronchi, lungs and pleura.

Stomach (gastralgia, gastritis, gastric ulcer), liver (jaundice, cirrhosis, and liver abscess) and peritoneum.

* Called also the uric acid filter group, for each local precipitation acts the part of a uric acid filter to the blood and tissue fluids of the rest of the body (see experiments mentioned further on)

Ovaries, uterus and pelvic fasciæ (uterine fibroma and other fibromata), epididymis, &c.

Fasciæ and fibrous tissues in neck, back, spinal cord and lumbo-sacral region, hands, &c.

Other fibrous tissues in the body, as of skin (eczema and psoriasis fibromata).

Intestines, cæcum, and appendix (flatulence, colic, enteritis, colitis and appendicitis).

Muscles (myalgia).

Nerves (neuralgia).

Teeth coverings (periostitis).

Uric Acid plus microbes acting together as in—

Catarrh, influenza, phthisis, pneumonia and malaria (its fever and sequelæ).

Glands, irritation and fibrosis of (not pyæmic).

B. The circulation or solvent group, due to excess of uric acid in the blood (collæmia), and its effects on the circulation, blood pressure and nutrition, as—

Headache, epilepsy, convulsions, chorea, hysteria, neurasthenia, nervousness.

Mental depression, excitement, mania.

Bodily depression, fatigue, lethargy.

Vertigo, syncope, insomnia.

Periodic paralysis, chronic paralysis.

Asthma.

Dyspepsia—dilated stomach.

Congestion of liver, glycosuria, diabetes.

Bright's disease, albuminuria, hæmoglobinuria, dead hands, cerebral hæmorrhage, cramps, dropsy, uræmia.

Gravel and calculus.

Neuritis.

Retinitis.

Cerebral degenerations.

Spinal degenerations.

Skin diseases, as—

Atrophy, ulcerations.

Raynaud's disease.

Diseases of vessels—

Purpura, thrombosis.

Degeneration, atheroma, calcification.

Aneurysm, morbus cordis (collæmia acting with strain and resulting in dilatation), angina pectoris.

Diseases of blood—
Anæmia, chlorosis.
Hæmoglobinæmia.
Leucocythæmia.
Pernicious anæmia.
Graves' disease.
Menorrhagia and uterine congestion, dysmenorrhœa.
Piles, pruritus ani et vulvæ.

All these can be expressed in two words—

A. Group = Gout.

B. Group = Collæmia.

Gout is relieved by solvents; collæmia by retentives. Both are prevented, relieved, or cured by a uric-acid-free diet.

Gout is accompanied by quick circulation, raised temperature and few granules in the blood.

Collæmia is accompanied by slow circulation, sub-normal temperature, and many granules in the blood.

This epitomises the subject.

With the exception of gout and rheumatism (A. Group), all diseases connected with uric acid are due to its effects on blood pressure and the interstitial circulation in the organs and tissues.

Thus headache, fits, mental depression, bad temper, vertigo, and a host of minor functional disturbances, represent the effects, direct and indirect, of high blood pressure on the intra-cranial circulation.

I wish it to be understood, however, *that while I consider uric acid to be often the most important cause of these disturbances, I do not allege it to be the only one;* and in the chapters which treat of the cerebral circulation, it will be evident that other causes may produce like alterations in the cerebral circulation, and therefore like symptoms.

The well-known symptoms of high blood pressure represent the effects of uric acid in obstructing the capillaries and raising the pressure in the arterial system behind them.

Asthma and chronic bronchitis (in part) probably represent some of the effects of high blood pressure and obstructed capillaries on the bronchial and pulmonary circulation, and this may explain the common relation between these diseases and gout and chronic Bright's disease.

Dyspepsia may undoubtedly be produced by obstructed capillaries in the stomach and intestines, which inhibit gastro-intestinal digestion, and substitute putrefactive processes, which again will explain at least part of the relationship between dyspepsia and headache,

epilepsy, and mental depression, or between dyspepsia, Raynaud's disease, paroxysmal hæmoglobinuria, and anæmia.

In the liver, as in the stomach or intestines, we may obviously get more or less stasis or congestion as a direct or indirect result of circulatory changes produced by uric acid.

The same thing applies to the kidney, and here we have a very tangible result of the changes so produced in its circulation, *i.e.*, the fluctuations of the urinary water previously referred to.

Now, any excess of water in the blood and tissue fluids is promptly excreted, while the circulation through the renal arterioles and capillaries is free.

But the circulation through the renal capillaries, which we must remember are doubled or reduplicated, may fail for two reasons: (1) that the capillaries are obstructed so that a normal heart cannot drive blood through them (as in collæmia), or (2) that the capillaries are normally free, but the heart is weak (strain, debility, morbus cordis), and has little driving power.

In either case there is retention of fluids in the blood and tissues, and in both the heart is not up to its work either absolutely or relatively.

In (1) we must treat the collæmia, in (2) the heart, taking care at the same time that there is no collæmia, for practically (1) and (2) often occur together.

The same thing is seen in the salivary and probably in all glands; and therefore when a uric acid headache is present and urinary water is scanty, the mouth tends to be dry or sticky and the saliva scanty; and when the headache has been cured by acids, opium, mercury, iodides, or any of the drugs which clear uric acid out of the blood—not only is there diuresis, but saliva also becomes relatively profuse.

And exactly the same thing applies to the excretion of water from the lungs, which rises and falls with urinary water and other secretions, and inversely with the uric acid.

There is little doubt that in the muscles collæmia produces deficient circulation and removal of waste products, though probably the disinclination for muscular exertion (so marked a feature in attacks of migraine or mental depression), is due partly to the condition of the nerve centres. Still, I think that cramps and other slight disturbances of muscle function are not improbably sometimes due to the deficient circulation of collæmia (see also the Causation of Fatigue in chapter viii.).

The circulation and nutrition of the skin are markedly influenced

by uric acid, both in physiology (fig. 5) and pathology, and hence the pallid and cold surface commonly seen in migraine. In conditions where there is for some time continual excess of uric acid in the blood (as in post-febrile conditions, marasmus, and chronic dyspepsia) the nutrition of the skin may be interfered with to an extent accounting for not a few eruptions (especially ulcerative), slow healing of wounds and other troubles; and in these conditions I order drugs that clear the blood of uric acid, in full confidence that, if there is no organic disease, I shall improve the nutrition of the skin and facilitate the healing of wounds and disappearance of rashes. This consideration explains the frequent connection between skin eruptions and menstruation, for menstruation is nearly always accompanied by a certain amount of dyspepsia with lowered nutrition and consequent collæmia (see chapter xii.).

The effect of menstruation on the excretion of uric acid has, however, a wider bearing on the causation of disease than the production of a few skin eruptions, and I therefore give a figure to illustrate the fluctuations it may produce,

Fig. 31 shows the effect on the excretions of normal menstruation in a woman aged 36 in ordinary health.

On November 13, the first day of menstruation, uric acid is fairly close to urea, and urinary water fairly high.

On the two following days uric acid rises and remains very high, and on the second of these days urea and water fall decidedly. Acidity follows the uric acid more closely than the urea, and its rise is probably much more the result of excess of uric acid in the urine than of any change in the alkalinity of the blood; indeed, with the fall of urea on the 15th, the blood probably became more alkaline. On the 16th uric acid falls, but rises again on the 17th, the last day of the menstrual flux. On the 18th and 19th it rises still further, but falls very decidedly on the 20th.

Urea and water rise steadily from the 15th to the 18th, and fall sharply on the 19th and 20th, this being very probably in part due to the high uric acid on the 18th and 19th.

On the 15th, with the high uric acid and falling urea, there was some decided headache, and on the 16th headache and increased irritability; on the 17th she felt better, but on the 18th there were distinct rheumatic pains, and it is possible that the rise of urea and of water on this day were due to some slight febrile movement accompanying the rheumatic pains. On the 19th she felt fairly well, but was taking some soda mint tabloids for the relief of dyspepsia and other minor troubles, and on the 20th there was some depression due to falling urea and the still rather high uric acid.

We see then that menstruation at its onset may be accompanied by a fairly normal excretion of uric acid, quickly followed by a very marked rise in excretion, which continues with some fluctuation right through menstruation, and even lasts for two to three or more days after the flow has ceased; that these rises of uric acid are accompanied by headache, irritability and depression, with some dyspepsia

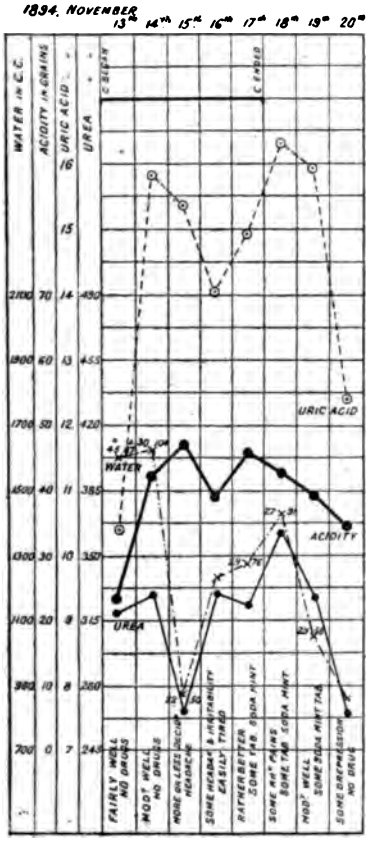

FIG. 31.—EXCRETION OF URIC ACID DURING MENSTRUATION.

and a marked fall of urea; in a word by the impeded circulation and diminished metabolism which collæmia produces.

With the help of my friend, Mr. A. G. Ewbank, formerly house physician to the Metropolitan Hospital, I secured the excretions in several cases during menstruation, and though they vary and in some cases are complicated by active disease, they indicate that

menstruation is generally accompanied by a plus excretion of uric acid, especially towards the end of the period, or just after cessation; while in cases where I got the excretion a few days before the period, it rather appeared as if its onset were accompanied by diminished excretion of uric acid and a period of stimulation. Unfortunately I was unable to get this in fig. 31, but the uric acid was in fairly normal position on November 13, the first day of the period.

It appears probable that menstruation causes a fluctuation in excretion of uric acid, a diminished excretion or retention before or at the beginning, followed by a corresponding plus excretion during the period and just after its termination.

These facts explain the connection between menstruation and such troubles as headache, epilepsy, mental depression, dyspepsia, skin eruptions, rheumatism and catarrh; in fact, we have here an epitome of the causation of disease by uric acid. Menstruation produces a fluctuation in the excretion of uric acid and in the amount passing through the blood; and the uric acid in the blood, by controlling the circulation, dominates the function, nutrition, and metabolism of the whole body.

So that preceding and at the beginning of menstruation we have a diminished uric acid excretion or retention with a free circulation, a rise of urea and acidity, and a general stimulation of function, nutrition and metabolism from which follows increased activity and well-being of mind and body. Neither headache, fits, depression, dyspepsia, nor catarrh occur at this time, but rheumatism, if present, may be slightly increased.

There then follows excessive excretion of uric acid, this excess traversing the blood, and, as a result, circulation is everywhere obstructed, nutrition and metabolism diminish, and there is a noticeable fall of urea; in a word, collæmia and its results. Headache, irritability and depression now occur, with fits if the patient is subject to them; dyspepsia begins, and skin eruptions appear or are aggravated, and there is a liability to the infection of cold. On the other hand, rheumatism is often distinctly better, as it always is, with a plus excretion of uric acid; and this explains the common alternation between rheumatism and migraine; what cures the one aggravates the other.

Dr. Oliver has noted, by means of the arteriometer, the high blood pressure of menstruation and the absemce of postural variation in this physiological condition, which resembles the similar absence of postural variation met with in the gouty and in migraine (see *British Medical Journal*, 1896, vol. i., p. 1375).

In fig. 31, after the first onset of collæmia and depression, there follows a rise of urea and acidity from November 15 to 18, and with this the headache and dyspepsia improve, but some rheumatic pains occur.

Later, collæmia again causes diminished metabolism, and the rheumatic pains give place to dyspepsia and mental depression.

There is one physiological connection of menstruation which may be found to explain a corresponding pathological section—the fact that the period is often accompanied by enlargement of the thyroid gland. Here we have three things together, probably of some importance; fluctuation in the excretion of uric acid with its temporary excess in urine and blood; resulting in a temporary period of high blood pressure, and, possibly in connection with this, the enlargement of the thyroid.

This is a side light on the causation of Graves' disease and its frequent occurrence in women, for its chief signs are but exaggerations of those occurrent in physiology, and the quick action of the heart may be but the ordinary effect of high blood pressure when it causes heart failure; in a word, Graves' disease may be a result of high blood pressure originating in the recurrent high blood pressure and collæmia of each menstrual period.

While considering this subject we must not forget the fact that at least one drug (chloride of calcium), which has some reputation for curing or relieving Graves' disease, has a very decided effect in lowering blood pressure, which it does by clearing the blood of uric acid.

Two cases recalled this to my mind, and decided me to make a trial of treatment for Graves' disease accordingly.

The most interesting of these was that of a young man, aged 22, sent to me by the late Dr. Maclaren, of Harley Street, his history showing that a few years ago, after much sedentary work and rather excessive smoking, he suddenly exerted himself violently, and afterwards suffered from attacks of palpitation and threatenings of syncope.

He was treated for heart weakness or strain, and after a course of Schott treatment the condition of the heart improved, and severe headache followed, apparently ordinary migraine (uric acid headache), to which he had been periodically liable since puberty.

This continued for some time, and he was able to resume his professional work, until after hard work and exposure his heart got weak again; the palpitation returned and the headaches ceased.

The Schott method was resumed with numerous tonics, raw beef juice, beef jelly, and a great excess of nitrogenous food.

The condition of the heart improved, and again the headaches returned, having been absent while it was weak.

When I saw him after this, my notes were as follows :—

"Decidedly pale, but fairly nourished. Eyes slightly prominent, and distinct fulness of the lower part of the neck, over thyroid region. Patient volunteered statement that he now had to wear collars ½-inch larger than a year ago.

"Pulse rate 96. Apex beat slightly outside the left nipple line. First sound reduplicated over the septum of the ventricles, and second sound loud both at apex and base.

"At present he is fairly well, and only had one slight headache about a week ago, which was cured by tea."

Such is a short outline of what I consider the most interesting medical case I have seen ; interesting not only for what it certainly reveals, but also in its suggestions.

I summarise it thus : cardiac strain from exertion following much sedentary work, and the muscular depressant action of tobacco in excess.

Relief of cardiac condition and return of headaches due to high blood pressure.

Relapse of heart and disappearance of headaches.

Relief of cardiac condition. Excess of nitrogenous food taken.

Present condition : some little failure and dilatation of the heart, headaches comparatively slight, pulse quick. And with these signs slight prominence of eyeballs and distinct enlargement of the neck (? early Graves' disease).

I have no doubt that there was chronic high blood pressure as shown by the old migraine. After the strain the heart failed and then recovered under treatment, only to fail again because the cause of the high blood pressure remained, while the ability of the heart to keep up the blood pressure alternately failed or was restored.

The condition when seen by me was one midway between severe cardiac failure and high blood pressure with severe headaches ; the pulse was quick, there was some dilatation of the heart and the headaches were comparatively slight in accordance ; and there followed signs suggestive of early Graves' disease.

Be this as it may, I cannot doubt that if the blood pressure had been reduced by a uric-acid-free diet from the time of his first cardiac strain, he would have recovered more quickly and permanently without the alternating signs of heart failure or headache, and would probably have also escaped the threatening signs of Graves' disease.

It is difficult to say how it may end and how far quickened heart's action, dilated heart, enlarged thyroid, and prominent eyeballs, point to incurable disease. The case is incomplete, but I give it for its great suggestiveness, and because it provides a convincing demonstration of the pathology of the uric acid headache, which may be read with what I say of the action of antipyrin in this headache in chapter vi.

With regard to prognosis, before I saw this case, the idea that Graves' disease might be a result of high blood pressure, occurring most frequently in women, because of their monthly fluctuation in blood pressure, had led me to put a hospital patient upon a uric-acid-free diet, and this even in a few weeks apparently gave relief, the pulse rate falling from 120 to 92, and the face becoming less congested. This case had been under observation several years, and had been given all the drugs considered useful (though ice to the thyroid seemed to do best), and had had the right lobe of the thyroid removed by my colleague, Mr. W. H. A. Jacobson, with the apparent result of lessening the prominence of the right eyeball. Still, in spite of all treatment, up to the time of altering diet the signs of progressive dilatation of the heart continued.

Sir T. Lauder Brunton points out in *St. Bartholomew's Hospital Journal*, December, 1897, p. 35, that Graves' disease is generally the result of shock or injury, and shock or injury produces collæmia, which may become chronic.

There is also a rather interesting parallel between Graves' disease and chorea (to the pathology of which I allude later), for both bear the same relation apparently to shock or injury and to the consequent collæmia. But in Graves' disease the collæmia produces high blood pressure, enlargement of thyroid, prominent eyeballs, and eventually heart failure; in chorea it produces obstruction in the circulation of some important nerve centres in the brain, and this is intensified by more or less heart failure.

Some have found a history of acute rheumatism in about 11 per cent. of cases of Graves' disease, and this is interesting, for if Graves' disease, as I suggest, results from collæmia, it probably bears the same relation to acute rheumatism as migraine, another collæmic disease; and chorea is similarly related to collæmia and acute rheumatism. Thus we see three diseases, migraine, chorea, Graves' disease, all due to collæmia and more or less similarly related to the acute arthritis produced when collæmia is terminated by retention.

Professor Murray points out in the *Lancet*, vol. i., 1899, p. 752, that while little or nothing is known of the pathology of Graves'

disease, most cases improved by treatment are generally given mercury in some form, and mercury is one of the drugs with most power in ending collæmia and lowering blood pressure. With the increased power over blood pressure gained in the course of these researches, I am confident that I can do much for Graves' disease either by drugs or diet.

In a later paper Professor Murray (*Lancet*, 1902, vol. ii., p. 1612) points out in connection with Graves' disease that exophthalmos is often absent. With regard to treatment, he says little about mercury and recommends no special diet, though he adds on two extra pints of milk daily. I fear this quantity of fluid could not fail to raise the blood pressure. I notice that he is disappointed in the results obtained with belladonna. This is not surprising, for it increases uric acid collæmia (see fig. 9).

In the *Lancet* of February, 1905, p. 347, Dr. D. Chalmers Watson, of Edinburgh, shows that the feeding of fowls on a diet of raw meat and water, produced very striking changes in the thyroid and parathyroid glands; and this interested me, because I know that in the human animal the thyroid enlarges with an increase of uric acid in the blood, a fact specially noticeable during menstruation in women who suffer from migraine. On the other hand, those who have had from any of these causes enlargement of the thyroid and who then take to the uric-acid-free diet, have, as collæmia diminishes and blood pressure falls, a decided and progressive diminution in the size of these glands.

In the *British Medical Journal*, 1903, vol. i., p. 1015, Dr. R. Llewellyn Jones writes on Graves' disease, in association with rheumatoid arthritis. This also is of interest, for Graves' disease and rheumatoid arthritis are both results of collæmia. The uric acid in the blood which raised the blood pressure, causing prominence of the eyes and enlargement and hypertrophy of the thyroid, also kept up chronic irritation of the joints and produced the rheumatoid changes. When the pathology of these diseases is rightly understood, it will be easy to control both by controlling the common factor.

I am glad to see that Dr. Hector Mackenzie (*British Medical Journal*, 1905, vol. ii., p. 1077), is opposed to the operation of thyroidectomy. I agree with him, because it seems absurd to remove a local result of a cause acting throughout the body.

I now believe that while an advanced case of Graves' disease is somewhat rare, the prominent eye or some degree of this condition is not uncommon, especially among the uric-acid-feeding upper classes, and may be seen perhaps in one or two out of almost any ten people.

The underlying cause common to Graves' disease and minor conditions of the prominent eye is high blood pressure. I consider the prominent eye a valuable symptom of this condition, and with the exception of certain alterations in the eyeball itself (such as those of myopia, which can easily be identified, or certain new growths or tumours either in the eye or neighbouring structures), blood pressure is the chief determining factor in the prominence or retraction of the eyes.

In extreme cases, we have the prominent eye of Graves' disease with blood pressure say 150 mm. of mercury or above, on the one hand, and on the other the sunken eye of the child dying of diarrhœa and collapse, with blood pressure probably 50 mm. of mercury and below, and the cold extremities, the shrunken skin and perhaps the deeply concave fontanelle. Between these extremes are intermediate conditions, so that the position of the eye is a ready guide in clinical medicine to the vascular condition of the patient, and its value is increased by measuring even roughly the extent of the prominence or retraction, and noting the other signs of the vascular condition to be seen in the face with each position of the eyeball. Graves' disease may, if taken in time, be relieved or even cured by removal of the high pressure, or its cause, uric acid collæmia. I will merely say further that of the three cardinal symptoms of Graves' disease, the prominent eye is seen frequently in the high blood pressure headache (migraine or uric acid headache), that enlargement of the thyroid occurs in most women during menstruation when blood pressure is raised, and when those who suffer from migraine or epilepsy have attacks, and that the quick pulse appears with all similar high blood pressure conditions as the heart begins to fail. Graves' disease is, in a word, an exaggeration of some of the common signs of high blood pressure.

Thus I know several who are sufferers from uric acid headache at each menstrual period, and with each of these attacks the neck enlarges so that for a day or two ordinary clothing cannot be used; and doubtless it is this monthly fluctuation in collæmia and its resultant blood pressure that accounts for the fact that exophthalmic goitre is chiefly seen in women; and weak persons or those nearing the period at which the heart tends to failure, may have more or less palpitation and quick pulse with each such attack, like the patient whose case is described above.

In all conditions of developing or established Graves' disease, where the prominence of the eyes is well marked, blood pressures of 150 mm. of mercury and above are the rule.

Now if an eye (where blood pressure is normal) is closed and a card held vertically over its centre, its edge will rest firmly over the supra-orbital ridge above and the malar and superior maxillary bones below; and it will touch the eyeball so lightly as to cause no discomfort.

And this is no doubt the natural position, for the bony boundaries of the orbit now afford the eye efficient protection from pressure and injury.

When, however, the card is thus applied to an eye which is too prominent, it rests on the front of the ball and rocks up and down over it, only touching one edge of the orbit, and makes a pale mark on the eyelid, causing painful pressure on the eyeball, without touching the upper and lower borders at the same time.

When the eyes are markedly prominent, one sees the whole side of the face forming a cone, of which the apex is the front of the eyeball.

In a normal face there is an upward and forward slope to the lower margin of the orbit, then a crateriform depression, with the ball of the eye projecting from the centre.

But in the other the depression above the margin of the orbit is obliterated, and the cone is continued without a break to its apex at the front of the eyeball.

The eye is so prominent that the lids stretch forward over it, obliterating the normal depression at the margin of the orbit.

And here, I think, is a point of difference between the eye of exophthalmic goitre and the prominent eye I am describing, for the eye in Graves' disease becomes prominent more or less suddenly, and the lids fail to cover it to anything like the normal extent; but in the prominent eye of chronic high blood pressure there has been more time, the change and increase of prominence has been gradual, and the lids have been able to follow the eyeball and cover it to a greater extent than in Graves' disease.

Among concomitant signs of the prominent eye the most important is a distended condition of the skin, whether with fat, blood, or serum, or all three more or less mingled; the wrinkles tend to be smoothed out, and the whole skin of the face gives the idea of distension.

This is well seen in a woman about 45, the skin of the face is puffy, the eyes stand out and the side of the face slopes up to them with hardly any indications of the orbital margin; with such signs at such an age it is probable that blood pressure is not below 150 mm. of mercury.

Minor conditions in some stages of the prominent eye are a distended condition of capillary vessels, giving a dark streaking of colour very different from the delicate flush of health, with no perceptible vessels.

The tense skin and prominent eye gradually give place to a more wrinkled skin and an eye which, though still prominent, shows now the margin of the orbit surrounded by folds of eyelid as the previous stretching relaxes, and this probably occurs at an age when the hair is becoming markedly grey.

Later still the eye is hardly prominent, the skin is still puffy, but in wrinkles and folds, the colour in the distended skin vessels becomes dusky and irregular, almost blotchy, as heart weakness and venous congestion increase. Finally, near the last stages of heart failure the face becomes pale, the blood retreating from the degenerated vessels, which gave the face what was supposed by the ignorant to be its hue of ruddy health, but was veritably the stamp of vascular degeneration.

With wrinkled but still puffy skin, a sunken eye, an orbital margin surrounded by loose folds, a paling surface and a shrunken appearance, we get a quick, irregular or intermittent pulse and a blood pressure little over 100 mm. of mercury.

Thus one woman has prominent eyes and puffy skin, with a decidedly stout face and figure.

An older woman with grey hair has a puffy skin, but the eyes are retracted rather than prominent, and her pale face, wrinkled skin and wasting figure denote heart failure and falling blood pressure; a single glance at these two tells us which has the lower blood pressure, and why.

Or one sees a woman who is obviously too excitable, and in her face the eyes are somewhat prominent and the skin puffy, but round them are large loose folds of skin, and the history of cause and effect is legible. Her blood pressure has been high for a long time, and is dropping; as her hair has grown grey the heart has failed, the eye has become less prominent, and heart failure and fall of blood pressure are causes of mental excitement, and even of mania (see chapters v. and viii.).

Or again, one sees a man with the above facial signs, who for years has suffered from periodical headache. Of late he has had less headache but some palpitation; his face corroborates what the palpitation denotes—that the heart is failing, and that as the blood pressure diminishes the headaches due to blood pressure are less severe.

Prominent eye is most common about 45 and 50 years of age, for then with good nutrition the heart attains its greatest hypertrophy; but it is seen early also, and I have recently seen a child of 9 or 10 with this symptom. The mother was in a more developed stage, and both suffered from high-blood-pressure headache.

High blood pressure tends to produce prominent eyes from the time of full growth when the heart attains full power: here doubtless is one reason the headache and epilepsy of high blood pressure are frequent at puberty.

This continuing, the eyes are most prominent in middle life when the heart is strongest, and prominence decreases as the heart fails with advancing years.

Taking two cases, if the obstruction to the circulation is equal the eyes will be most prominent with the stronger heart, indeed, it is often possible to gauge approximately the thickness of the left ventricle from the varying prominence of the eye.

Naturally conditions hindering circulation through the lungs (bronchitis, asthma and emphysema) will increase prominence, for these not only directly obstruct the circulation, but defective oxygenation of the blood causes collæmia, and also, directly and indirectly, obesity. Coughing, straining and heavy exertion alike raise blood pressure and increase the prominence of the eye; on the other hand deep breathing lowers blood pressure and diminishes prominence. Hence breathing exercises when unclothed are good for all who suffer from high blood pressure and obesity, and tight clothing increases their trouble.

Confirmation of this comes to hand in the fact that a special form of corset placing the waist at the brim of the pelvis instead of over the lower ribs and diaphragm appears to aid materially the process of respiration and thus to diminish the tendency to local and general obesity. With constriction over the diaphragm and lower ribs the respiratory power of the individual thus compressed must be diminished in proportion to the extent of the pressure, but if pressure is placed at the brim of the pelvis and lower part of the abdomen the diaphragm and lower ribs are free to act to the full extent of their muscle power in inspiration. Such a corset I recently saw which had seemingly produced a remarkable improvement in respiratory power and diminution of obesity.

From these facts it is obvious why women who lace tightly suffer from deficient respiratory power, collæmia and obesity. Indeed, it is in such persons the full effects of these causes are seen. But it is also clear that those eschewing corsets may nevertheless suffer

in the same way if any defect in lung power (such as pleurisy produces) or some weakness in structure or function of the heart prevents free circulation and correct oxygenation of the blood, and thus acts in the same manner as the restrictive corset.

Indeed, if one member only of a family is stout, it is safe to suspect either tight clothing impeding the action of the diaphragm, or some defect in lungs or heart—producing defective combustion, collæmia and obesity.

Naturally persons so circumstanced increase the evil by a diet introducing the very substance which blocks the circulation.

Mental excitement also raises blood pressure and thus accentuates prominence.

Absence of these troubles and presence of good respiratory power may, however, to some extent mask the effects of blood pressure on the eye and render it less prominent; but good respiratory power also tends to prevent very high blood pressure, and to diminish the tendency to obesity.

A tendency to fat doubtless increases this prominence and the distension of the whole face and body; still, high blood pressure so constantly accompanies obesity that I take obesity as an indication of its presence, or rather as a result of the defective circulation which causes the high blood pressure. Hence we often find obesity accompanied by glycosuria or albuminuria; these being forms of defective combustion due to defective capillary circulation, which tend to occur together as results of a common cause, the prominent eye being the facial sign of the first effect of this cause—high blood pressure.

In estimating the prominence we must remember that folds of puffy skin round the orbital margins may make it appear less prominent, and in such cases we must feel the margin of the orbit and correlate the position of the eyeball. But allowing for these things and for differences of face and of size and prominence of bony ridges, there is no doubt that the position of the eye is often a valuable guide to blood pressure; and with some of its associated facial conditions a constant sign of collæmic circulation.

Not everyone having high blood pressure from collæmia will suffer from headache; this presupposes a certain size and arrangement of vessels at the base of the brain; and among sufferers there are many variations in the height of blood pressure at which pain begins. Some suffer at anything over 130 mm. of mercury, others at 160, and others have little or no headache with the highest blood pressures known.

Again, not everyone with collæmic high blood pressure develops asthma, glycosuria, or albuminuria; these may only appear when some concomitant circumstance precipitates the stress of the altered circulation on lungs and bronchi, liver, or skin. But the underlying condition common to all is collæmia and its high blood pressure, and varying prominence of the eye is a useful index of this condition.

It not only indicates high blood pressure, but it often shows how long it has been present, and whether the heart has steadily hypertrophied under it, has failed early before much hypertrophy was possible, or after it had for years sustained a very high blood pressure.

Observing not only this, but the surrounding skin, whether tense round an eye almost starting from its socket, or lying in folds round one less prominent, or wrinkled and unduly lax over an eye scarcely prominent at all—we often read in the face not merely varying blood pressure, but no unimportant part of the history of the vascular system.

Constrast the effects of normal pregnancy with those of menstruation. Here is a steady upward progression of nutrition and metabolism; urea and acidity rise and the blood is consequently kept clear of uric acid.

For this reason in normal pregnancy all diseases due to an excess of uric acid in the blood, such as headache, fits, mental depression, dyspepsia, asthma, &c., are conspicuously absent, while Sir A. Garrod (prev. ref., p. 212) tells us that pregnant women occasionally suffer from gout. Not only so, but there is a popular belief mentioned by Sir W. F. Wade (*British Medical Journal*, 1872, vol. ii.) which I believe to be well founded, that pregnant women do not readily take diseases, such as colds, fevers, &c. Opium, in freeing its devotees from collæmia, offers also temporary and similar immunity from disease, and bracing climates or athletic training have the same effect. Normal pregnancy, therefore, corresponds with the stimulation stage of menstruation, and the diseases of both are alike. But if pregnancy is not normal, or metabolism be upset by such a disturbance as vomiting, the case is altered; there is no rise in urea and acidity. They fall, the blood is flooded with uric acid, and the diseases due to this—headache, fits, depression, dyspepsia, asthma—are present or increased; the patient is liable to take colds and fevers, and if the upset of metabolism is at all severe, that last and worst stage of defective combustion, Bright's disease, may appear.

I give a case in chapter xiii. where such a disturbance of pregnancy, possibly increased by altered pressure relations in the abdomen, and some heart failure, apparently originated this disease.

The point as regards infection is briefly thus: in normal conditions, and still more in those of stimulated nutrition, with the blood free from uric acid and the circulation in consequence perfect in all the tissues, when digestion is satisfactory and metabolism complete, when the fires of life burn strongly, the microbes of disease are consumed and become innocuous.

When under reverse conditions, however, combustion is incomplete and the fires smoulder, the microbes are established and multiply.

The causation of fever is thus of extreme interest, for fever is accompanied by increase of combustion and metabolism. Have we here a protective effort on the part of nature to stimulate the fires of life and burn out the invader? It is interesting to note that Loewy and Richter (*Berl. Klin. Woch.*, March 1, 1897) found that fever artificially produced protected animals to some extent against microbe inoculation.

Summarising, we may say the effect of excess of uric acid in the blood is deficient combustion, while the result of keeping the blood clear by any means at our disposal is complete combustion.

Previous writers have stated, and it is still said, that the excess of uric acid in the urine in these conditions is the *result* of deficient combustion; my researches make an almost absolute demonstration that the truth is the exact reverse, and that uric acid is the *cause* of deficient combustion.

At the end of pregnancy, however, especially if labour is tedious and fatigue great (see Fatigue, chapter viii.), the fire burns low, the uric acid retained during pregnancy passes into the blood and acts as a depressant, and lactation causes further debility and collæmia. Under these conditions all or any of the diseases conspicuously absent during normal pregnancy return in an aggravated form.

I must mention that fig. 31 serves to explain observations made by others upon the effect of menstruation on metabolism; thus in an article on "Stoffwechsel Während der Menstruation," by T. Schrader (in von Noorden's *Beitrage zur Lehre vom Stoffwechsel*, 1894, Heft. ii., S. 132), it is pointed out that menstruation is accompanied by a constant fall in the output of nitrogen by the fæces and urine, which is not the result of alteration in diet, but which Schrader thinks due to a diminished formation of urea.

He gives an explanation seemingly incomplete. I must refer my readers to the article, but I think this diminished production of urea is evident in fig. 30, and its causation, by the deficient combustion and metabolism invariably produced by uric acid in the blood, sufficiently clear.

I believe it to be a universal law in physiology and pathology that high uric acid connotes low and falling urea, and low uric acid rising and high urea, and this law lies at the root of such conditions as fatigue in physiology, and of many pathological blood variations up to Bright's disease itself. It was through overlooking this effect of collæmia on the formation and excrêtion of urea that the physiologists were led into wrong conclusions regarding the relation of urea excreted to force produced. Thus in spite of the knowledge that albumen is a *sine quâ non* of life, they accepted the false idea that force could be got out of various non-nitrogenous substances, and never noticed that non-nitrogenous substances produced force merely by calling out the reserves of albumen already in the body (See chapter viii., also "Diet and Food," ed. vi., p. 37).

Lastly, the stimulation which accompanies the sexual act in men has an effect on nutrition and excretion of uric acid almost identical with that of menstruation in women.

The sexual act is no doubt a powerful stimulus to circulation, and is accompanied by muscular activity, but this is not pushed to the fatigue point, and consequently produces a rise of urea and acidity, which is the first effect of all exercise, and lasts until perspiration reduces acidity.

This rise of urea and acidity clears the blood of uric acid and produces a stimulation of nutrition and metabolism resembling that at the beginning of menstruation, but (as in menstruation and in the action of a long list of drugs), this primary retention of uric acid is followed by a secondary plus excretion; and during this stage of the fluctuation a man will suffer from similar troubles to those affecting the end of menstruation, and this is the reason that many men who suffer from the uric acid headache (migraine) often have an attack on the day following sexual intercourse (see chapter vi.).

I consider it a fact of some interest that the sexual appetite appears to increase with high and rising blood pressure, and to be slight or in abeyance with low or falling blood pressure, and as the sexual act itself tends to produce the latter, it removes the desire for repetition.

Further, I think that as the sexual act produces low and falling blood pressure, it necessarily relieves conditions which are due to high and rising blood pressure, such (for instance) as mental depression and bad temper. We probably have here a connection between conditions of high blood pressure with mental and bodily depression and the act of masturbation, for this act will relieve those conditions, and therefore tends to be practised.

We must bear this in mind in such cases, and where they are obviously associated with high blood pressure, we should more wisely assist Nature in lowering this pressure, than attempt to oppose her with moral suasion. In a word, we should treat the morbid circulatory conditions, and leave morality to right itself when a satisfactory cerebral circulation has been restored by the use of suitable diet or drugs.

The connection between sexual appetite and blood pressure, or (what is the same thing) the mental conditions its variations produce, have been noticed by opium-eaters in whom these changes are seen to perfection, in whom also they are due, as elsewhere, to changes in the amount of uric acid in the blood, where they can be controlled by controlling the uric acid, as, for instance, by means of salicylate (see fig. 15, and remarks on it).

Thus in "L'Encephale," 1887, p. 306, we are told by an opium *habitué* that during the stage of opium well-being, in which, as we know, the capillaries are free and blood pressure low (see fig. 35B), there is no desire for women, and that difference of sexes ceases to exist; but that later on in the stage of rebound, misery, high blood pressure (see fig. 35A) and craving for a fresh dose of the drug, desire for women is great, and that contact brings calm with it, though the act can be repeated many times.

These effects of the sexual act on blood pressure account, doubtless, for the calm and good temper which follow the act, and also probably for the storms of passion in either sex if the desire is not obtained, and the high blood pressure not relieved. These in turn may account for not a few of the murders and suicides of every-day life (see chapter viii.) so obviously connected with the sexual relations.

Here my remarks about masturbation apply, for a person under the dominion of collæmia and high blood pressure is not accountable, and is indeed temporarily insane. Let us recognise it as useless to appeal to the *mens insana*, while leaving untreated the *corpus insanum*.

I strongly recommend all who are interested in the causation of disease by uric acid to read the article just referred to; it gives a most able summary of the evil effects of excess in the blood, as well as the opposite effects of its more or less complete absence; it shows also clearly that the necessary increase of dose is due to the retention of uric acid, which is ready to return to the blood the moment the acidity falls, and as opium diminishes appetite and therefore produces wasting, increased help is continually required to keep acidity from falling.

It demonstrates also that the action of opium in averting common diseases is the exact parallel of that of normal pregnancy and the reverse of the second stage of menstruation, being due to its preventing collæmia and keeping the fires of life at white heat.

I note also that Mr. Havelock Ellis* considers that sexual climaxes may fairly be regarded as ultimately a physiological reaction to cosmic influences, among which he reckons the annual fluctuations in the excretion of uric acid.

The annual curve of the conception rate in Europe, with its marked rise in April, May, and June (prev. ref., p. 297) must correspond very closely with the maximum excretion of uric acid in early summer, and is a remarkable confirmation of what I have said. I shall refer to some other curves showing the maximum incidence of suicide and insanity in London, and of general paralysis in Paris in the same month. I believe they have one causation, and hence their time association; a point we shall better understand after discussing the circulation problems of uric acid.

That collæmia affects the nutrition of the extremities as well as the skin is seen in the pale, cold hands and feet which are so marked a symptom in migraine, in the "dead hands" of Bright's disease, and the still more marked alterations met with in Raynaud's disease.

Last, but not least, excess of uric acid seems to produce changes in the nutrition and structure of the blood itself, so that as it is possible to cure anæmia by giving iron, it is possible to produce anæmia by giving uric acid, and where the two are given together the uric acid overpowers the iron, and the blood either remains in *statu quo* or deteriorates. In my own person not only does my blood fraction $\frac{\text{hæmoglobin per cent.}}{\text{red cells per cent.}}$ vary in value hourly and daily with the uric acid passing through my blood, but it is possible to vary it at pleasure by giving uric acid or iron.

Recalling the effects of uric acid on the blood, and the effects of menstruation on uric acid as shown in fig. 31, I pass on to fig. 32, a temperature chart of Mary H., aged 18, who was in the Royal Hospital for Children and Women, suffering from chlorosis, in October, 1894.

At first her temperature was slightly raised, as is common in such cases, and varied between 98·2° and 99·6°. She was put on bismuth and Carlsbad salts for some dyspepsia, and on the 7th these were stopped, and she was put on pulv. ferri. carb. gr. x. three times a day. On the 13th the temperature became more

* "Studies in the Psychology of Sex," vol. ii., p. 121.

irregular, with an evening rise and morning fall, and this continued on the 14th and 15th. On the 14th menstruation began and lasted till the evening of the 16th. On the 16th temperature was normal both morning and evening. On the 17th it passed below normal and remained there till the evening of the 21st, when it rose to 99·6°, and on the following nights did much the same, only falling below normal once on the morning of the 24th.

The pulse during the first thirteen days ranged from 72 to 102; during menstruation it was 108 on one day and 102 on another; during the subnormal temperature which followed on the 17th, 18th, 19th and 20th its highest rate was 96. Pulses of 66 were recorded on two mornings, and it once again fell to 66, with the subnormal temperature on the morning of the 24th.

I examined her blood on the 10th, 17th, and 24th. On the 10th

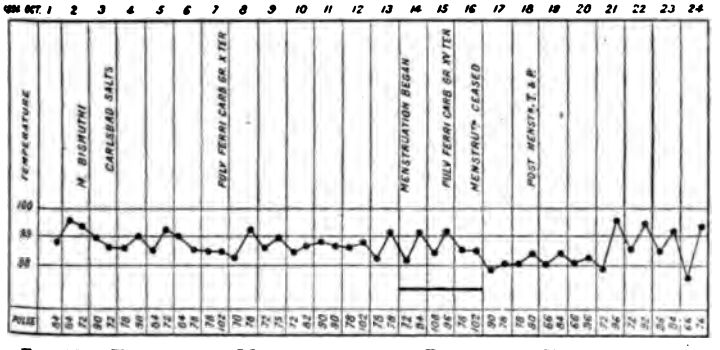

FIG. 32.– EFFECTS OF MENSTRUATION ON PULSE AND TEMPERATURE.

hæmoglobin was 35 per cent. and cells 120 per cent., $\frac{35}{120} = \cdot 29$. On the 17th hæmoglobin was 41 per cent., and cells 121 per cent. = ·33, a rise of ·04; and on the 24th hæmoglobin was 46 per cent. and cells 130 per cent. = ·35, a rise of only ·02.

The object of this figure is to show the slight rises of temperature which precede and accompany menstruation, and the following subnormal temperature and slow pulse, and to draw attention to the remarkable fact that while the blood decimal improved ·04 in the week ending October 17, it only improved ·02 in the week ending October 24, in spite of the fact that iron was continued the whole time, and was indeed increased to grs. xv. three times a day on the 15th.

This is my explanation of these facts: the rises of temperature on the 13th, 14th and 15th were due to the stimulation, with

retention of uric acid, that preceded and accompanied menstruation, which produced, perhaps, a little rheumatism or other result of the storage of uric acid. On the 16th the temperature became normal, denoting that the minus excretion of uric acid was giving way to rebound and a plus excretion, and the subnormal temperature on the 17th, 18th, 19th, 20th and morning of the 21st showed that the plus excretion and the corresponding excess in the blood continued.

On the 21st the uric acid rebound ceased, urea and acidity rose, and some of the remaining uric acid was driven out of the blood into the joints, causing the evening rises of temperature near the end of the figure, and such rheumatic pains as would correspond with those of November 13, in fig. 31.

It seems probable, then, that there was diminished excretion of uric acid just before and during the two days of menstruation, that this was followed by a rebound or plus excretion on the last and four following days, and that these changes in the quantity of the uric acid in the blood accounted for the fluctuations in temperature, and for the fact that the pulse was at its quickest on the second day of menstruation, and at its slowest on the following days of low temperature; for the temperature is lowest in those hours of the day in which there is most uric acid in the blood, and highest in those evening hours when there is least (fig. 5); the pulse, too, is slowest when there is most uric acid in the blood, and quickest when there is least.

Pulse and temperature, therefore, point to excess of uric acid in the blood from the 17th to the 21st, and the blood decimal apparently agrees; for I have shown not only that my own blood decimal varies hourly and daily with the amount of uric acid passing through the blood, but that in chlorosis the blood decimal curve may be moved at pleasure by controlling the uric acid (see figs. 53 to 57); and the fact that the blood decimal rose ·04 between the 10th and 17th and only ·02 between the 17th and 24th, is evidence that there was some excess of uric acid passing between the two last-named dates.

I believe that menstruation will often be found to yield temperatures very similar to those in fig. 32, and I have many similar curves; the low temperatures corresponding with low urea, headache and depression, as on November 15 and 20 (fig. 31), and the high temperatures with the high urea and rheumatic pains on November 18.

With reference to the relation of sexual activity to the seasonal alteration of the excretion of uric acid, and the high blood pressure which collæmia produces, I believe that some increase of sexual feel-

ing in women is commonly present in the days following the menstrual flow, and this, as we see from fig. 32, exactly corresponds with some collæmia and its high blood pressure and low temperature.

In reference to fig. 31, I have met with several cases in which women suffered from pain in the abdomen of the nature of colic, due, I believe, to gout of the intestines (see chapter x.) coming regularly month after month, even for years, just 8-10 days after a period and corresponding, I have no doubt, with the rheumatic pains which others experience, as on the evenings of the 5th, 6th, 7th and 8th days after the period in fig. 32. This pathology has several times been justified by success in treatment.

Sir W. F. Wade makes the interesting remark that menstruation relieves the headache, depression and other signs of chlorosis, but they return afterwards and are worse (*British Medical Journal*, 1872, vol. ii., p. 35). This certainly refers, (1) as regards improvement, to the early period of stimulation corresponding to the raised temperature, October 13, 14 and 15 (fig. 32), and to the low uric acid, November 13 (fig. 31); and (2) as regards the subsequent deterioration, to the subnormal temperature in fig. 32 and to the high uric acid in fig. 31.

Sir W. F. Wade likens these effects to those produced by venesection, and says that venesection relieves, but that after each repetition the symptoms return more quickly and severely.

It is not difficult to see why a venesection should relieve, for every similar loss of blood is followed by a rise of temperature—probably the result of the blood being cleared of uric acid by the venesection tending to reduce its alkalinity and therefore its power of holding uric acid in solution.

This might raise the question whether the rise of temperature from the 13th to the 15th was not due to the loss, but this figure itself shows us that the temperature was raised before this began, and that it fell to normal on the 16th before the loss of blood had ceased.

When the excretion of uric acid exceeds the relation to the urea excreted along with it of 1-35 there is some excess of uric acid in the blood (collæmia), and this is proportional to the extent by which uric acid exceeds this relation to urea, and proportional also to the absolute quantity of urea. Thus an excretion of 1-25 on a total urea excretion of 350 grs. a day will furnish 4·0 grs. of uric acid for passage on that day, while an excretion of 1-25 in relation to an excretion of 600 grs. of urea will furnish 6·9 grs. of uric acid. And it appears that the obstruction of capillaries, and all the secondary

symptoms and phenomena are proportional to the absolute quantity of uric acid present in the blood from hour to hour.

If urea varies only with body weight, and does not exceed the physiological level (3½ grs. per pound per day), uric acid will vary only with body weight, and the amount available will be relatively the same in all cases. But if a man takes more animal food than is required to keep urea at the physiological level, he will not only introduce more uric acid than the man who only takes what is necessary, but he will also form more, just as he forms more urea, and will in both ways come to have a larger quantity available for solution in his blood. Hence the evil effect of living almost entirely on animal food, as some people have accustomed themselves to do. On the other hand, urea can be kept about the required physiological level if those foods containing large quantities of uric acid or its equivalents are not taken. The normal formation of uric acid in relation to normal urea will be harmless if the unnecessary introduction of uric acid is kept as low as possible, and these two points—sufficient urea without unnecessary uric acid—must be the aim of diet treatment in these diseases.

In place of rheumatism and gout I see one disease, an arthritic irritation due to the presence of urates. This in some circumstances may be limited to one joint (gout), or may affect several joints and possibly the heart also, either contemporaneously or in succession (rheumatism).

Ebstein and others have shown that the introduction of urates in solution into the tissues produces local irritation, and it appears that the irritation is greater when the urates are in solution than when deposited in solid form. Indeed, it is no uncommon thing to find in the *post-mortem* room a toe-joint plastered with urates when the patient had complained of no local irritation, and even given perhaps no history of gout. They had evidently been there some time, and had caused no trouble. On the other hand, the ingestion of a little acid wine or beer will cause, say, often within half-an-hour, retention of some urate (probably in solution) in certain joints, which from hard work or previous irritation are less alkaline, and thus bring about considerable pain and inflammation, which whether it is called gout or rheumatism, is due to urate irritation. I have scores of times produced some such irritation in myself, knowing every step in the chain of causation; and having this knowledge, I have recognised the causation of joint irritation in gouty or rheumatic patients, by drugs given by others, or myself, for other purposes.

I will undertake to produce an arthritis, clinically indistinguishable from gout or rheumatism, in any member of the profession who

is in good general health. All that is necessary is to get a little uric acid into the blood, and when the defective capillary circulation, high blood pressure, slow pulse, scanty urine, and more or less headache and mental depression show that it is actually present, administer as quickly as possible some acid or other drug which interferes with the solubility of uric acid, and drives it from the blood into the tissues (see cases in chapter xvi.). It will probably be also necessary to work or produce some slight irritation in, or in the neighbourhood of, the joints to be most affected. Thus a man who gets gout because he drinks some extra beer on Saturday night, gets it in the wrist of that hand which he has used most in his trade, and we must follow Nature to this extent if we wish to reproduce the clinical picture of gout. But it is the same with all the other diseases I have mentioned; each one can be produced or intensified by the intentional introduction of uric acid into the blood, bearing in mind the laws which govern its solubility. So that if anyone doubts whether headache is due to uric acid he has only to swallow certain quantities of the substance under conditions which do not interfere with its remaining in solution, to convince himself. The same method may be used for the investigation of many other diseases, and I have applied it to investigate the causation of anæmia (chapter xii.).

In attempting to estimate the effects of uric acid on the metabolism of the body as a whole, it must never be forgotten that the depressant effect tends to increase itself, so that when the ball is set rolling it will go on. Thus uric acid is commonly in excess in the blood, because it is more than usually alkaline (*i.e.*, a more than usually good solvent of uric acid); but the effect of an excess of uric acid in the blood is a diminution of the capillary circulation in all the organs and tissues, and results of this are, among other things, diminished digestion and absorption of food, diminished interchange between the blood and the tissues; that is, a general slackening of metabolism; and this in turn causes a lessened formation of urea, and of acids and acid salts which usually keep pace with urea. But falling acidity of the urine means increasing alkalinity of the blood and (so long as plenty of urate is available for solution) more and more marked collæmia; and thus depression of mind, body, and metabolism increase indefinitely. But if, before depression of metabolism has led, as it ultimately does, to much atrophy of tissue, a drug is given which clears the blood of uric acid, the process may be completely reversed, for when the blood is cleared of uric acid there is again a free circulation; digestion and absorption of food are resumed, and free metabolism in the tissues proceeds; the forma-

tion of urea and of acids rises, a steady and progressive metabolism is started, and the blood is kept clear.

I am often asked whether the effects of small doses of drugs which clear the blood of uric acid are not out of all proportion to the quantity taken; why does a very minute dose of a nitrite, a few grains of a sulphate, or a small fraction of a grain of calomel, free all the capillaries, cure headache or mental depression, and alter the whole condition? Truly the effect is disproportioned to the dose, and much more uric acid may be retained than a fraction of a grain of calomel could possibly combine with.

But the explanation is easy if we remember that each of these drugs, supposing it clears the blood of uric acid for only a minute or two, starts an upward metabolism which progresses long after the direct effect of the drug has ceased.

The drug is like the percussion cap in the cartridge; it does not furnish the force which drives the bullet; it supplies the spark which ignites the powder. That an apparently insignificant dose sometimes produces severe and long-lasting pains in the joints is analogous, the drug having started a process which continues after its action ceases.

We must remember that uric acid retained locally tends to act as a filter, and to retain all uric acid at hand, therefore when such a filter action begins the blood may be cleared for some time.

It has been suggested by several of my critics that I have been led by personal interest and experiences to attach undue importance to the *rôle* of uric acid in production of disease. It has often, indeed, appeared to me probable that I might not escape this error. Yet, in considering my position, I can honestly say I have spared and still spare no pains to subject all my assertions to the most rigid tests, and that I made none until the evidence appeared to be extremely strong.

I have been, therefore, delighted to find that uric acid taken by the mouth is at once absorbed and added to the urates in the blood and tissues, as this supplies the means of applying the experimental method to the uric acid causation of disease.

I thus obtain not only the convenience of experimenting more accurately on myself; but anyone who doubts the power of uric acid in variations of circulation, nutrition and metabolism, can easily test most of the points in his own person.

It is now possible for anyone to slow capillary circulation, raise the blood pressure, slow the pulse, and reduce urine per hour by swallowing uric acid. But it must be remembered that the first effect is to raise the acidity of the urine and diminish the alkalinity of the blood, so that uric acid is cleared out of the blood, and the

excretion in the urine is diminished. While this is occurring blood pressure is lowered, the pulse and capillary circulation are quickened, and excretion of urine increased, for which reason a dose of uric acid will temporarily cure a uric acid headache. Next day, however, or whenever the acidity falls, uric acid passes in excess into the blood, and collæmic symptoms appear.

I regard such a practical experiment as an infinitely better guide to the effects of uric acid on the capillaries than an injection of any quantity into the vessels of animals.

For even if, say, 10 grs. of uric acid were injected into my own blood stream, a freeing of capillaries and a fall of blood pressure rather than a rise would result, and further, unless my blood had been previously rendered strongly alkaline, this uric acid would not remain in it more than a very few moments, but would be retained in the liver, spleen, joints and other tissues, causing some gouty pains probably, but no rise of blood pressure.

To affect blood pressure with uric acid it must be introduced and passed through the blood in combination with an alkali.

The introduction of an alkali into the blood will, however, produce no effect on blood pressure if there is no uric acid for combination purposes, while mere absence of uric acid from the blood, owing to previous removal by excretants, will occasion free capillaries, lowered blood pressure, quick pulse, profuse urine, and improvement in the blood decimal value (see also Fatigue, chapter viii.).

I summarise by saying that uric acid acts as a factor in causation of disease in one of two ways:—

(1) As a direct local irritant when present in any tissues in considerable quantity and probably still in solution or suspension as a colloid quadriurate (see next chapter).

(2) As an obstructor of capillaries, affecting the circulation, nutrition, function and temperature of all the organs and tissues of the body, and producing high blood pressure, directly affecting the heart and the vessel walls, and otherwise influencing the intra-cranial, thoracic and chylopoietic circulations.

It is chiefly as an obstructor of capillaries that I shall treat of uric acid in the following chapters.

By this action on the circulation it controls physiology, and determines the slow or quick combustion of the human body, just as shutting or opening the flues determines that of the kitchen fire.

The old theory (that excess of uric acid in the urine is the result of deficient combustion) explains nothing, but this newly-acquired knowledge (that deficient combustion is caused by that excess of

uric acid in the blood of which excess in the urine is an index) explains everything.

With this knowledge power over physiology is doubled, and power over pathology trebled and quadrupled. Indeed, in fields of the treatment of disease where empiricism formerly reigned, something approaching mathematical accuracy can now be substituted.

In a number of disease processes it is literally true that when we have controlled uric acid we have controlled disease; and what must be deduced from preceding chapters are the ways and means for controlling uric acid; and in following chapters the action of uric acid in each disease.

In every case we should be able to stop its action; but removal of results must depend on their nature as well as on the tissues affected. We should, for instance, be able to dissolve and remove urates from any tissue in the body: but the place they have occupied will be filled by a scar and not by normal tissue, for pouring water on the fire will not rebuild the ruins. Therefore, though increase of knowledge strengthens our power over disease, it is far from absolute, and prevention is much better than cure.

Persons ingesting uric acid with meat and tea may be thus divided: (1) Those who are frequently ailing, and in ailing days excrete nearly all the uric acid stored in the preceding period of health (as, for instance, a patient who remarked after two years on diet, "Now I am always well, on the old diet I was never well"). They do not accumulate much, and as a rule do not suffer seriously, hence, perhaps, the saying that creaking doors hang longest. (2) Those who with strong digestions and vigorous nutrition are well for fifty or sixty years and then suddenly break down; these accumulate in their bodies large quantities of uric acid, and when nutrition begins to fail with advancing age it rushes into the blood and then pneumonia (see chapter ix.), Bright's disease, or cerebral hæmorrhage suddenly supervenes. Even here there have been probably not a few warning signs, which if heeded would have made it possible to prolong life.

It is always unsafe to swallow uric acid, but in some its effects are almost instantaneous; in others they may be deferred for years, and then come with accumulated force. This is a question of solubility.

Those who have retained most take longest to get free, hence as a rule the cure of arthritis is slower than that of collæmia.

The effect of uric acid on metabolism is first to stimulate and then to depress, and both are results of its mechanical influence on capillary circulation.

CHAPTER V.

Uric Acid and the Circulation.

Dr. Liveing records ("Megrim or Sick Headache," p. 329) that the pulse during an attack of megrim is slow and of high tension (see fig. 44). And soon after I discovered that by influencing uric acid I could produce or remove the headache, I also noticed that in altering uric acid I automatically altered the rate and tension of the pulse; I therefore eventually formulated the conclusion (*British Medical Journal*, January, 1889, p. 291) that, "*cæteris paribus*, arterial tension varies with the amount of uric acid circulating in the blood," with the rider that, in so far as it depended on uric acid, I could alter it in either direction.

I thus acquired the belief that uric acid not only accounted for the headache, but also for the high tension pulse and cold extremities, and that as it obstructed the capillaries, and so raised the tension, it produced slowing of the pulse, in accordance with Marey's law that pulse rate varies inversely as arterial tension. He says, "Le cœur bat d'autant plus fréquemment qu'il éprouve moins de peine à se vider," and explains that the chief obstacle to the heart's systole is the resistance "que le sang éprouve à s'ecouler des artères dans les veines à travers les petits vaisseaux." Again; "La vitesse du sang augmente si la force du cœur augmente, ou si la resistance des petits vaisseaux diminue," and he expresses the effect of the arterial tension, produced by the resistance in these little vessels on the rate of the heart's action, by saying, "le cœur précipite ses battements à mesure que la tension arterielle leur fait moins d'obstacle." ("Circulation du Sang," pp. 315-336.)

As to the signs of "forte tension arterielle," he mentions "pulsations rares, le cœur se vide difficilement, le pénétration du

sang dans les artères est lente—le dicrotisme n'a que peu d'amplitude" ; and again, " Le resserrement des petits vaisseaux, cause primitive de cette tension élevée des artères, se traduit par le diminution du volume des extrémités par la moindre coloration des teguments, par l'abaissement de la temperature périphérique " * Briefly—all the signs of uric acid headache and related conditions.

If my premisses and deductions are sound and uric acid influences the circulation as I believe, it follows that it dominates the function, nutrition, and structure of the human body to an unimagined extent, and instead of affecting the structure of the few comparatively insignificant fibrous tissues in which it is found after death, it may direct the development, life history, decay and dissolution of every tissue, from the most important nerve centres and most active glands, to the matrix of the nails and the structure of the skin and hair.

Turning to physiology, we find the excretion of uric acid varies inversely as the acidity of the urine. Figs. 1, 2 and 3 serve to demonstrate this, and as regards pathology and drug action a few hours' work such as that shown in fig. 3 will suffice. Take a dose of citrate of potash, and as the acidity falls uric acid will rise, or take an acid, and as acidity rises uric acid will fall, and the corresponding effects on the capillary reflux will be visible.

As regards physiology, the large excretion in the a.m. and early p.m. hours (fig. 3) is familiar, for the late Sir W. Roberts (" Urinary and Renal Diseases," p. 71) tells us that the quantity secreted during what he has called " the alkaline tide " is three times as large as at other periods. Those who have followed my description of fig. 3 will have seen that this is not due to increased formation of uric acid, but to the previous storage or retention in the tissues during the high acidity period of the previous night, and that the quantity of uric acid excreted on any given morning is proportional to this and to the fall in acidity of the urine. They have seen also that by altering the acidity of the urine (that is, the alkalinity of the blood), any large excretion of uric acid in the morning hours can be prevented.

But in physiological conditions there is a large excretion of uric acid in the morning, and for reasons given in the description of fig. 3, the uric acid producing this large excretion traverses the blood on its way to the kidney, while in the later p.m. hours there is a low excretion of uric acid, and the blood is more or less free.

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* Prev. ref., p. 549.

It follows from this, and reasons previously adduced, that uric acid is in excess in the blood during certain hours daily, and more or less completely absent during certain hours of each evening and night (fig. 3).

Uric acid is in excess daily from about 4 or 5 a.m. to about 2 p.m. (see figs. 2 and 3), and is more or less completely absent from about 2 p.m. to midnight. There is occasionally a slight rise of uric acid above urea in the afternoon hours, 3.30 and 6.30 p.m., represented probably in fig. 3 by the slight fall of acidity at 5 p.m. and between 6 and 10 p.m., but this varies with diet, exercise, and other factors, and need not now detain us.

If arterial tension varies with the amount of uric acid circulating in the blood, and if, as Marey shows, arterial tension or blood pressure controls the rate of the heart's action, it follows that the pulse in physiological conditions will be slower and of higher tension in the a.m. hours and up to about 2 p.m., and quicker and of lower tension in the p.m. hours up to about midnight.

I cannot doubt that this is the case. I am confident that all clinical observers will uphold this statement, and Marey himself says: "On observe le matin au reveil un ralentissement du pouls avec tous les caractères de la forte tension: le soir contraire le pouls s'accélére et présente le caractère de la tension faible." ("Circulation du Sang," p. 350.)

Again, if pulse rate is a measure of arterial tension or blood pressure, and this is (other things equal), a measure of the obstruction of capillaries, it follows that the capillaries are most obstructed in the a.m. hours and freest in the p.m. hours.

We have fairly abundant evidence that this is the case, for, according to Marey, the difference of temperature in the rectum from that in the mouth is a measure of the contraction of the vessels of the skin; the greater the difference of these temperatures the greater the contraction of the skin vessels and *vice versâ*. In fig. 5 it is observable that these temperatures, in physiological conditions, are far apart in the a.m. hours up to 2 p.m. or rather later, and much closer together in the p.m. hours, proving that the skin vessels are relatively obstructed in the former and free in the latter, which is in absolute accord with the physiological fluctuations in the excretion of uric acid as shown in fig. 3.

Independent proof exists that the capillaries are obstructed in these same hours in another important organ of the body, namely, the kidney, for fig. 3 shows, in common with nearly all excretion curves in this volume, that urine is scanty up to 2 or 3 p.m., and tends to be profuse in the p.m. hours.

It has been shown that the flow of urine may be stopped by faradising the central end of the vagus nerve, which causes contraction of the renal vessels (*British Medical Journal*, "Epitome," 1895, p. 104), so that contraction diminishes the flow of urine, and dilatation increases it.

Obstruction of renal vessels, therefore, in physiological conditions is greatest when excretion of uric acid most exceeds its normal relation to urea, and is least in the evening and night when uric acid is furthest below its normal relation to urea.

In the case of the kidneys there is evidence that the renal capillaries are directly obstructed by uric acid in the blood, and the

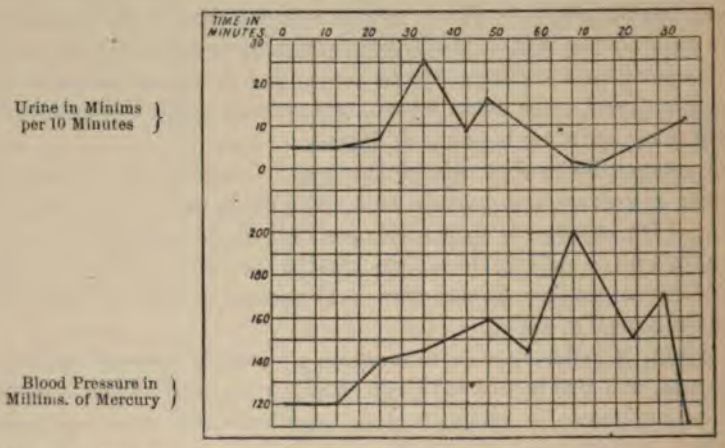

FIG. 33.—CURVES SHOWING THE EFFECT OF ERYTHROPHLÆUM UPON THE BLOOD PRESSURE AND SECRETION OF URINE.
(From Sir T. Lauder Brunton's paper in *Phil. Trans.*, vol. clxvii.)

possibility of an intermediate factor is negatived by the fact that the urinary water varies hourly and daily throughout life (and alike in physiology, drug action, and pathology), inversely with the height of the uric acid above its normal relation to urea.

The consequence is that in controlling uric acid, excretion of water by the kidney can also be controlled, and we have to some extent seen in chapters ii. and iii., that nearly the whole group of so-called diuretic drugs furnishes instances of this law, for they produce diuresis and also altered blood pressure, pulse rate, temperature, formation of urea and liberation of physiological energy by clearing the blood and urine of uric acid; while if for any reason they fail to clear the blood, none of these effects appear.

If uric acid diminishes excretion of urinary water by obstructing the renal capillaries, it follows that drugs with like action, such as digitalis or erythrophlæum, in contracting the arterioles and raising tension, should produce a like result. I have quoted from Sir T. Lauder Brunton's researches, showing that this is the case. He says ("Pharmacology and Therapeutics," ed. iii., p. 430): "Thus Mr. Power and I found that on injecting digitalis into the circulation of a dog the blood pressure rose, but the secretion of urine was either greatly diminished or ceased altogether. Here it is evident that the renal vessels had contracted so much as to prevent the circulation through the kidney, notwithstanding the rise that had taken place in the blood pressure. After a while the blood pressure began to fall, and then the secretion of urine rose much above its normal, showing that the general blood pressure was then able again to drive blood into the kidneys."

And Sir T. L. Brunton's figure of the excretion of urine during the action of erythrophlæum, which he has kindly allowed me to reproduce, indicates the same thing (see fig. 33).

In the case of digitalis, and other drugs of similar action, the diuresis has been wrongly credited to the rise of pressure, with which Sir T. L. Brunton's figure and facts show that it does not completely correspond. The first effect of these drugs is to retain some water, and then, as the arterioles are relaxed and blood pressure falls, this passes out, producing a marked temporary diuresis.

Digitalis and erythrophlæum thus parallel what occurs in the uric acid headache, in epilepsy, hysteria, and other conditions of high tension pulse and obstructed capillaries. While the capillaries are obstructed and pressure high, the water is retained in the blood and tissues, but later when the capillaries are freed and pressure falls, it passes out in a more or less copious diuresis, and urinary water is thus inversely as uric acid excretion, and inversely as obstruction of the capillaries.

We shall see that the capillaries of the lungs are obstructed in the same way and in the same relation to the excretion of uric acid as those of the skin and kidneys, and what has been said about the excretion of water from the kidneys might be applied to that from the lungs, for both of these vary together, in physiological and pathological conditions, inversely with the height of the uric acid above urea in the urine.

These facts alone, to say nothing of the striking evidence from other tissues and organs, suffice, I think, to prove that high arterial tension or blood pressure in man, occurring either physiologically or

pathologically, is due to obstruction of capillaries, and that the most important cause of this obstruction is the presence of a relative excess of uric acid in the blood stream. See also figs. 64 and 66, for the changes in pulse rate and blood pressure.

There are no facts against this explanation of what has been observed, and hundreds in its favour; for not only does it explain innumerable events in physiology and a still larger number in pathology, but it provides power (hitherto unknown) to control these events and sequences.

Having thus concluded that excess of uric acid in the blood stream produces obstruction of capillaries throughout the body, we may consider the manner of its action.

I have nothing definite to offer, but I believe that we shall gain by keeping the more probable ways in our mind's eye.

(1) Uric acid may act like digitalis, or erythrophlæum, and these we learn from Sir T. Lauder Brunton (previous reference, pp. 996 and 273), act locally on the vessels of an artificial circulation, and in the case of erythrophlæum, after division of the cord, so that all question of action on the vaso-motor centre is removed.

(2) It may act directly on and through the vaso-motor centre.

(3) There is a third possibility, though I believe this has never been suggested by anyone except myself. Should it work out, it might come to much the same thing as the local action theory No. 1.

It was suggested by watching, as I have done for years, the extremely tedious filtration of the gelatinous urate of silver through the asbestos fibre filter as used in Haycraft's process for the estimation of uric acid (see chapter xviii.).

I reflected that if the capillaries resembled in any way the interstices of that asbestos filter, if uric acid were present in the blood stream in some similar gelatinous form, and if the heart had to drive it through these capillaries, it might have great difficulties to encounter, and might occasionally meet with partial failure.

In other words, the obstruction thus produced in the capillaries may be mechanical and not vital.

To test this possibility, I took some kidneys and, fixing a cannula in the renal artery, measured the quantity of water or salt solution that poured out of the renal vein in a given time and under a given hydrostatic pressure.

I then added small quantities of finely divided oatmeal, flour, mud and other things, and watched their effect on the flow.

And lastly, I took some gelatinous urate of silver, washed it free from chemicals, and added it to the solution. I found that it had a

far more powerful effect on the circulation than the other substances, and comparatively small quantities sufficed to stop almost completely the flow from the renal vein.

As regards the quantity of uric acid in the blood, if we have say ·035 per cent. urea in the blood, or 30 to 35 grs. in the whole quantity (10 pints), and uric acid, as in the urine, in the relation to it of 1 to 35, then there may be normally in the blood about ·001 per cent. of uric acid or one grain in the whole quantity.

This quantity of uric acid might correspond with an average number of granules, say 1 to 15 red cells (see p. 91), and when the granules are to red cells as 1 to 1 we should have ·015 per cent. of uric acid in the blood, and it appears from the figures given on p. 76 that about twice this quantity may occur in some pathological conditions (cerebral hæmorrhage).

In the urine you may get 18 grs. in say 50 ozs. of water, or about 7 grs. to a pint, which is 1 in 1,250, and this, even when diluted with three volumes of water (1 of urine in 4, or 1 of uric acid in 5,000) greatly blocks the asbestos filter.

It is not greatly to be wondered at that uric acid in the blood in the proportion of 1 in 87,400, or 1 granule to 20 or 25 red cells, considerably blocks the capillary blood paths, and given a strong heart, causes a blood pressure of say 100 mm. of mercury; whilst 1 granule to 1 red cell, or uric acid in the blood in the proportion of 1 to 5,823, causes a blood pressure of 150 mm. of mercury.

The condition in which uric acid causes obstruction is probably when it is in solution in the normal phosphates of the blood stream, in which there are also present some alkaline salts of potash or soda. We know that uric acid or urates in solution with phosphate of soda in a test tube, will, when cooled or treated with other chemicals, deposit in a similar colloid or gelatinous form; and it is possible that in the blood something of the same kind occurs when there is a change of solubilities, or a balance, as it were, between alkalies and acids. The action of salts of lithia, for instance, makes it practically certain that it is upon the neutral phosphates of the blood that the solubility of uric acid in that and probably other fluids, chiefly depends.

This condition of the blood may be compared to a snow shower in the atmosphere, when the crystals come in large or small groups and finally in a storm, obstructing the highways. For convenience I shall give it the provisional name of collæmia, to be used as an equivalent to uricacidæmia, when I discuss the powers of urates in obstructing the capillaries.

Such floating masses of colloid in the tiny blood paths must, even when not very numerous, greatly hinder capillary circulation, and they may adequately account for all the phenomena of obstruction as seen, for instance, in the skin in migraine, and of high blood pressure as measured in the radial artery, while they will account for several otherwise inexplicable points in the connection of disease with the excretion of uric acid in the urine.

Mr. J. E. Saul, F.I.C., who has kindly undertaken from time to time to examine conditions affecting the solubility of this colloid uric acid, has brought out some points which, if not entirely new, are well worth remembrance while we consider the question.

It appears that uric acid or urates, in solution with phosphate of soda, will throw down a bulky colloid precipitate if rapidly cooled, or if the solution is rendered faintly acid ; a similar solution of alkaline urates does not give an immediate precipitate on cooling, but on addition of a little acid a colloid precipitate is at once thrown down. And this colloid precipitate is said to consist of a combination of acid urate of sodium and uric acid, the so-called quadriurate of Sir W. Roberts.

Speaking broadly then, there are two things which will bring down colloid uric acid in the test tube, one being cold and the other slight acidification.

It appears probable that the acidification acts in the tube as I have pointed out that acids act in the body, *i.e.*, they convert a certain amount of the neutral phosphate of soda (a solvent of uric acid), into acid phosphate of soda (not a solvent), so that some of the uric acid is precipitated ; and if this is so the effect of a given dose of acid will depend on the amount of neutral phosphate of soda it meets in the blood, just as I have shown (again with Mr. Saul's help, see chapter ii.) that the effect of a given dose of lithia depends on the amount of phosphate it meets.

It seems there is a certain point where there is a balance between acid and alkali (depending also somewhat on the quantity of phosphates) when colloid uric acid tends to be thrown out in the blood stream just as in the glass test tube (*collæmic point*). But if, when this condition is present in the human test tube, you give an acid you get such a decided precipitation of uric acid that it is caught up in the liver, spleen and fibrous tissues (gout), and the blood is rapidly cleared, just as it is generally relatively clear in acute gout, or still more markedly in acute rheumatism ; the urine now contains less than normal, and blood pressure falls because the capillaries are free. If, on the other hand, an alkali is given when there is coll-

æmia from a balance of alkalies and acids in presence of phosphate of soda, blood pressure remains high and urine scanty and full of uric acid, and this continues whilst alkali is given, and as long as there is any uric acid for solution. If the supply ceases and the alkali is continued, there is eventually a fall of blood pressure and a diuresis.

This at first seems as if solubility in the blood formed an exception to that in the test tube, in that alkalies prevent the precipitation of colloid uric acid in the glass, and yet alkali in the blood does not lower blood pressure. But I think the exception apparent rather than real; for if in a condition of collæmia we give an alkali, this may indeed dissolve some of the precipitate in the blood, but as its effect is also to bring fresh uric acid into the blood from the liver, spleen and fibrous tissues (reversing the action of acids in driving it out of the blood into the tissues), the condition of collæmia may remain much as before until the supply of uric acid fails, and then, as we know, capillary reflux quickens and blood pressure falls, though the alkali is continued.

When the supply of uric acid fails there is a diuresis in spite of the alkali, just as there is a diuresis under salicylates when the excretion of uric acid is falling.

The storage of uric acid in the liver and spleen (retention) has exactly the same mechanism as its retention in any other fibrous tissue in gout or rheumatism. In all these conditions the blood is relatively clear of uric acid and the granules are few.

When the fibrous tissues of the liver are less alkaline than the blood, uric acid tends to collect upon and around them just as in the fibrous tissues of the great toe; in these and all fibrous tissues there is constantly throughout life a retention of uric acid when alkalinity is diminishing, and a corresponding solution and excretion of uric acid when alkalinity is increasing, this accounting for the almost momentary fluctuations in its excretion in the urine, and the correspondingly frequent fluctuations in capillary reflux and blood granules.

Some* writers find this process incomprehensible; but I consider it simple enough, for uric acid is always present in solution round the colloid granules, and the dissolved uric acid tends to pass in one direction or the other through the membranes of the body according to the ordinary laws of the diffusion of crystalloids.

This law is here conditioned by the well-known fact that uric

* Dr. A. B. Conklin, *Milwaukee Medical Journal*, July, 1902, p. 192.

acid attracts uric acid, as, for instance, a little thrown on a filter will almost completely clear a urine of uric acid, even if only poured quickly through it once or twice.

This attraction is dependent on the amount of alkali present in the urine, and I have made some experiments to ascertain this point.

The fact that uric acid thus attracts uric acid has been demonstrated for years in every waterless urinal; for the moment a urine falls on a crust of uric acid or urates it leaves behind as an addition to the crust from one half to two-thirds of the contained uric acid, according to its acidity.

But an alkaline urine deposits no uric acid; on the contrary it resumes some from the deposits over which it passes; though as urines are generally acid the deposits on the urinal increase.

The same thing probably occurs in all the fibrous tissues as well as in the liver and spleen. When there are accumulations or deposits in the fibrous tissues of the liver, and the blood and tissue fluids round them are slightly alkaline, the accumulated uric acid attracts more from the blood and fluids; on the other hand, when the blood and fluids are highly alkaline they absorb uric acid from the deposits.

Hence gout and rheumatism occur in those special fibrous tissues which, from the action of acids, cold or local injuries, are least alkaline when the blood contains much uric acid.

All the uric acid traversing the slightly alkaline part is held and retained, hence Sir A. Garrod's observation, confirmed by my own (see p. 76), that blood drawn from an inflamed area contains little or no uric acid.

This can be demonstrated as regards the liver and spleen, and appears in all my figures of the results of swallowing uric acid. When this occurs and the blood is not well supplied with solvents the excretion in the urine does not rise, for all the uric acid swallowed must pass through the liver, and there meets with other uric acid and is retained. Hence there is no increase of uric acid in the blood, no slowing of capillary reflux, no increase of granules; whereas if solvents are supplied (salicylates or alkalies) the uric acid swallowed is able to pass the liver and arrives in the urine grain for grain; the capillary reflux is slowed and the granules in the blood increased.

In illustration I will briefly cite a few facts. A morning urine, full amber, clear, sp. gr. 1024, and slightly acid, contains ·084 per cent. of uric acid; the same passed through the uric acid filter contains ·06048 per cent., a slight loss because it is slightly acid.

The same urine with 10 per cent. of dilute acetic acid added when filtered yields only ·03024 per cent., the increase of acidity causing a great loss by retention.

The same urine, made alkaline to the point of precipitation of the phosphates by means of a little solid caustic potash, during filtration takes up an enormous amount of uric acid from the filter (about six times its original quantity) and is found to contain ·5376 per cent.

Another morning urine, sp. gr. 1026, containing ·08736 per cent. of uric acid, and after filtration ·0672.

The same urine made alkaline with liq. ammoniæ gives ·06048 per cent. of uric acid, the ammonia acting as the reverse of a solvent. We know that ammonium and its salts are injurious in gout and rheumatism, and do not increase the excretion of uric acid.

The same urine with as much phosphate of soda added as it will dissolve in the cold, when passed through the filter yields ·10752 per cent. of uric acid, thus demonstrating that the phosphate has acted as a solvent.

An evening and night urine (amber, clear, sp. gr. 1017, acidity neutralised by 4·3 cc. of decinormal soda solution to 10 cc. of urine) yielded ·05376 per cent. of uric acid, and after passing the uric acid filter ·02633 per cent. Note the smaller original quantity in the night urine and the greater proportional retention on the filter owing to higher acidity. The morning urine yielded only $\frac{1}{4}$ of its uric acid to the filter, the night urine yielded almost exactly $\frac{1}{2}$ of what it contained; the exact parallel of what occurs in the body: the night serum tends to throw out a little uric acid, leaving it in the joints and fibrous tissues of the body; the day serum (especially that of the morning) tends to take up a little uric acid from the same joints and fibrous tissues and pass it in excess in the urine. So that the condition of the urine in relation to the uric acid filter is a reliable index of the condition of the blood serum during the hours of its excretion.

The same urine, with bicarbonate of potash added, took up a little from the uric acid filter and yielded ·0672 per cent., and after the addition of a similar quantity of bicarbonate of soda ·07056 per cent.

The small difference between these two I attribute to difference in rate of filtration, for absolute identity in this matter is scarcely possible; a slightly thicker filter paper may cause slower filtration, and a solvent will take up or a precipitant throw out more uric acid on to the filter.

But in no case can these little differences in rate of filtration account for the enormous differences between the effects of acids and alkalies; it is only in the case of salts, having a small action either way, that slight causes of variation are of consequence.

The same urine with the addition of a little citrate of potash (gr. xv.) yielded after filtration ·02016 per cent., and after a similar amount of acid tartrate of potash ·02352 per cent.

But this urine, plus a small quantity of decinormal soda solution stopping short of complete neutrality, at once took up a large quantity from the uric acid on the filter and yielded ·10752 per cent.

On another occasion a urine of 4 p.m. containing ·08064 per cent. of uric acid, after passing through the uric acid filter, diminished to ·07056. When mixed with two or three grains of carbonate of lithia, it took up a considerable quantity of uric acid from the filter, and then contained ·13440 per cent. Lithia therefore acts fairly strongly as a solvent in glass, and, as we have seen, it is not a solvent when administered by mouth, only because it never reaches the uric acid in the body.

Another night urine (sp. gr. 1012, acidity neutralised by 2 cc. of decinormal soda solution to 10 cc. urine) before filtration contained ·03024 per cent. of uric acid, after the filter ·02352 per cent., a relatively slight loss, probably owing to lower sp. gr. and greater dilution as compared with previous specimens.

The addition of grs. iii. of sodii carb. to 25 cc. of urine gave after passing the uric acid filter ·18816 per cent. of uric acid—a great increase.

The use of a similar quantity of magnesii carb. yielded ·14784 per cent. of uric acid.

The addition of grs. iii. of urea caused a yield of ·03024 per cent., *i.e.*, it appeared to some extent to prevent retention by the uric acid filter.

The addition of salicylate of soda almost up to saturation yielded ·09408 per cent.

And the same experiment repeated with somewhat quicker filtration yielded ·06048 per cent.; in both the salicylate clearly acting as a solvent.

The same urine with sodii salicyl. almost to saturation and with 8 per cent. of dilute acetic acid yielded ·0672 per cent. of uric acid, that is, the acid slightly increased rather than diminished the solvent effect of salicylate.

This is interesting, as it is the exact parallel of what occurs in the body, where acids rather increase the excretion of uric acid under salicylates.

Salicylates also act best in acute conditions with fever, when the alkalinity of the blood is low, and act inefficiently in chronic conditions with debility, when the alkalinity is high.

For the same reason they act well in cold seasons and cold climates, badly or not at all in hot seasons and in warm climates.

Again, an evening urine, full amber, sp. gr. 1030, acidity neutralised by 9 cc. of decinormal soda solution to 10 cc. of urine.

Uric acid before filtration, ·08064 per cent.

After filtration, ·04704 per cent.

25 cc. of the same urine with 2 cc. acid acet. dil. gives after filtration ·02688 per cent.

The same plus acetic acid, also salicylate of soda nearly to saturation, yields after uric acid filtration ·1008 per cent.

The same with 11 cc. of decinormal soda solution yields ·1512 per cent. after filtration.

The same with soda solution as above and salicylate of soda almost to saturation yields ·24192 per cent.

The above experiment shows the great effect of a salicylate in overcoming the retentive action of an acid; for the acidulated urine yielded $\frac{3}{5}$ of its uric acid to that on the filter, while the same acidulated urine with salicylate of soda added, yielded nothing to the filter, but on the contrary took up from it extra uric acid to the extent of $\frac{1}{4}$ of the original quantity. So that the total solvent power of the salicylate was here equal to ·07392 per cent.

There seems to be no interference between alkalies and salicylates here in strong solutions, as the result of their combined action is if anything more than the sum of their separate effects; but this does not hold for more dilute solutions of these solvents, and their combined effect is then very decidedly less than the sum of their separate effects.

The same urine with addition of 5 to 6 per cent. of borax yields ·1344 per cent. of uric acid.

An evening and night urine, amber, clear, sp. gr. 1017, acidity equal to 3 cc. of decinormal soda solution to 10 cc. of urine, yields ·04704 per cent. of uric acid.

The same urine plus salicylate of soda in the proportion of 1 to 46 by weight, yielded after filtration ·04032 per cent., *i.e.*, there was no solvent effect, and I had previously found that small quantities of salicylate were neutral.

If I diminished the acidity of this urine to $\frac{3}{4}$ of the original quantity, it became almost neutral to the uric acid filter and yielded ·04032 per cent.

I then prepared a mixture in equal parts of the two urines, so that it contained half the amount of salicylate and half the amount of alkali, and the result one would have expected to be equal to ·04032, but I only got ·02688.

I then, using the same urine, doubled the amount of salicylate that produced ·04032, and got after filtration ·05376.

I also doubled the alkali and got ·0504.

I then doubled both alkali and the salicylate in a specimen of the same urine, and expected the result to be about 0·5376, but it was only ·03024.

This seems to show that where these solvents are present in such small amounts that there is only a slight solvent action, the result is not equal to their united action, but to something less; instead of causing a slight solution, the effect of mixing the two solvents (salicylates and alkalies) is to diminish their action and cause a slight retention.

This is much what we see in the living body, namely, that if salicylates are losing power and alkalies gaining, there is what I have called "a dead point" between the two, a decided retention of uric acid producing occasionally a somewhat disastrous relapse in the arthritis of gout or rheumatism.

It is obvious why salicylates act well in conditions of fever and high acidity of urine, for acids do not diminish, but rather increase their solvent powers; also why they act feebly in conditions of debility and with slightly acid or alkaline urine, for alkalies diminish their solvent powers.

These solvents cannot be present in the blood except in somewhat dilute solutions, so that such experiments furnish a complete explanation of their action.

It is obviously wrong to let patients perspire, or to wrap the joints in cotton wool while salicylates are given. Alkalies and heat pull together, salicylates with fever or with cold and acids go together; but to mix salicylates with alkalies or heat is a fatal mistake, and often accounts not only for their failure to do good, but for their injurious action (see cases in chapters ix., xvi. and elsewhere).

We can range the above substances in the order of solvent power somewhat as follows: First come the alkalies, potash, soda and magnesia, next their carbonates, and behind them their bicarbonates, solvent power obviously falling as the amount of alkali diminishes; next come the salicylates in strong solutions, and lastly borax and phosphate of soda.

Among the notable things assisting retention are acids, liq. ammoniæ, citrate of potash and acid tartrate of potash; the two last no doubt act as solvents in the body, but that is only after their conversion into carbonates, which are powerful solvents.

The action of liq. ammoniæ is interesting, as its effect in clearing the blood of uric acid and relieving migraine and depression is familiar; and even the inhalation of diluted ammonia fumes will produce quite a marked improvement in some of these conditions.

Some evidence that alkalies have a solvent action in collæmia is kindly furnished by Dr. T. Wilson, of Wallsend-on-Tyne, who reports that his headaches have been cured by my diet, and that his own remedy was bicarbonate of soda when the attack was coming on, and this always gave relief in from five to ten minutes.

Acting on this, I tried some bicarbonate of soda for a slight headache with undoubted effect, but as I took it in warm water, I am still in some doubt whether the hot water or the alkali did good, for both heat and alkali would tend to prevent collæmia.

I have since seen many cases in which somewhat large doses of alkali relieved uric acid headache by rendering the colloid more soluble, and therefore less capable of blocking the capillaries.

The following experience elucidates these points, One day when I was taking an alkali and had got my urine almost continually alkaline, I was feeling very well (as I thought) because there was little or no uric acid to get into solution in the blood, I took some rhubarb for lunch, and very soon after was taken with a slight but distinct headache. I suppose that on an alkali I was well, not because I had no uric acid in the blood, but because with plenty of alkali I was on the alkaline side of the collæmic point, and that the rise of acidity after lunch, reinforced by the acid of the rhubarb (see fig. 66), brought the blood to the neutral or collæmic point, causing a rise of blood pressure and headache. Dr. Wilson, it is interesting to note, regards acids as poisons, and records several instances in which the taking of vinegar or an acid wine, such as sherry, seemed to bring on an attack of headache. And it is quite possible that if the alkalinity of the blood is high, or he had been taking an alkali, the acid would bring his blood to the collæmic point and produce a headache, as the rhubarb appeared to do with me. And such a headache might be cured either by taking more acid to clear the blood of uric acid completely, or by taking an alkali to escape the collæmic point in that direction.

I have seen quite a number of patients who assert that a dose of an ordinary acid mixture brought on a headache, though a much

larger number have had headaches thus prevented or cured. Yet the report of the minority may have been just as true as that of the majority.

I have notes of several cases in which an attack of asthma was relieved by a dose of sodii bicarb., a difficult matter to explain unless by the above considerations (see chapter ix.).

When I had frequent headaches and much uric acid, alkalies would produce or increase headache, but possibly I did not take enough alkali to combine with the uric acid present and carry it beyond the collæmic point.

If this is correct, we see that the cause of the onset of headache or depression, with high blood pressure, in the early a.m. hours is the gradual change of reaction from the acid tide of the night, through the collæmic point to the alkaline tide of the morning, which may coincide with plus alkalinity of the blood and low acidity of the urine. I believe that the pulse is often slower and blood-pressure higher about 5 or 6 a.m. (time of collæmic point) in spite of being warm in bed, than an hour or two later, though the lowest acidity of the urine may not be reached till about 8 or 9 a.m. (see fig. 3).

During the lowest acidity of the urine and the greatest alkalinity of the blood (9 a.m.) there may be more uric acid in the blood than during the collæmic point (6 a.m.): but as some is in better solution owing to the larger amount of alkali available, there may be less collæmia and blocking of capillaries at 9 a.m. than at 6 a.m.

Therefore there may be less high blood pressure, headache and depression at 9 a.m. than at 6 a.m., though the amount of uric acid in the blood is greater at the former hour than at the latter.

And this is one of the conditions under which collæmia is not co-extensive with uricacidæmia.

Again, the low blood pressure and soft pulse resulting from continued muscular exercise may be due to the solution of the collæmia by the plus alkali and increased temperature, as well as to lowered pressure produced by increased area of circulation in the muscular tissues. When exercise has ceased, and acidity of the urine is rising and alkalinity of the blood falling, it passes again through the collæmic point, with headache, depression, and high blood pressure of fatigue in cases where there is enough uric acid to produce severe collæmia, and as a matter of fact this fatigue can be put off by taking an alkali, provided the quantity of available uric acid is not large.

Another point which it may explain is the value of alkalising the

urine (with citrate of potash, for instance) in acute Bright's disease (*cf.* the late Sir W. Roberts "Urinary and Renal Diseases," ed. iv., p. 436), for this not only lowers blood pressure by dissolving some of the colloid, but also renders the substance of the kidney alkaline, and so prevents retention and aids excretion of uric acid.

As a test I gave, in a case of chronic Bright's disease with high blood pressure and slow pulse, enough citrate of potash to alkalise the urine almost throughout the twenty-four hours; but this, though continued for more than a week, neither increased the urine, lowered the blood pressure, nor quickened the pulse, at least to any marked extent; while iodide of mercury subsequently very distinctly quickened the pulse.

Most of these points require much further investigation, but many things now indicate that collæmia causes high blood pressure, and this serves to explain more or less completely several facts otherwise inexplicable. There is no doubt that the uric acid headache is relieved by warmth, such as plunging the hands and feet in hot water, and probably the real explanation is the effect of the warmth in preventing collæmia, thus reversing the effect of washing the hands in cold water in Raynaud's disease.

Some evidence that an alkali may help to dissolve collæmia so long as no more uric acid is present than it can hold in solution, is to be seen in the cases of epilepsy (chapter vii.) treated with an alkali by Dr. C. Mordhorst, of Wiesbaden, as well as in the case, also recorded, when an alkali given to a gouty patient apparently produced epilepsy (see also remarks on these cases and on the paper of Dr. Ackermann in the same chapter).

I have seen a South American patient, who said that while there he could eat a large quantity of meat; but if he did the same in this cold country he suffered terribly from depression, and had thus been obliged to limit his quantity. As a result of former excess, he would have retained a large amount of uric acid, but the warm climate might tend to prevent collæmia; whilst here, even if less uric acid passed through his blood, there might be more severe collæmia owing to the precipitating action of the cold.

I believe also that when there is much uric acid, exposure to cold causes severe collæmia, and this with such a paralysing effect on circulation and nutrition that depression of nutrition and metabolism must ensue. Some cases of mental depression are much worse in the cold weather. On the other hand, when there is little uric acid cold stimulates; it raises the acidity of the urine and lowers the alkalinity of the blood, clearing it of uric acid like an acid, and

improving nutrition and metabolism. This is probably the explanation of the fact that persons on a fleshless or uric-acid-free diet feel the cold less than those who take flesh constantly. Cold is a stimulant to the former, but as it helps to cause severe collæmia in the latter, it damps rather than stimulates. These considerations also explain its effects on the nutrition of the skin and the important part attributed to it in the production of Bright's disease by the late Professor Semmola.

We must always remember that cold has a double action in precipitating uric acid in the blood: (1) the direct action of cold as in the test tube, alkalinity being unaltered, and (2) cold, by diminishing the excretion of acids in perspiration, diminishes the alkalinity of the blood.

To overcome its effects alkali must be very plentiful, for it must not only counteract retention of acids in perspiration, but also the direct precipitating effect. Hence in cold weather alkali must be supplied to take the place of sunshine or an extra coat.

This treatment would not suit a meat-eater because his supplies of uric acid are constant; whereas on diet they are easily kept in solution by a little alkali. And the circulation curves at once indicate the absence of alkali, for cold causes retention, followed by a rebound quite visible in the curves of capillary reflux and blood pressure (see fig. 40).

I never advise those on diet to keep themselves cool, on the contrary, I advise them to keep warm and avoid retention; since warmth will not depress and fatigue them as it does the collæmic meat-eater (see "Physiology and Pathology of Fatigue," chapter ii. of "Diet and Food").

I notice that Herz (*Wiener Klinik*, June and July, 1896, *v.* abstract in the *British Medical Journal*, epitome, November 28, 1896) points out that the smallest vessels, whose walls are not muscular, pulsate more vigorously the greater the rigidity of the tubes connecting them with the heart, and argues that the degenerative processes cannot, as supposed by Gull and Sutton, begin in the smallest vessels, but must be secondary to changes in the arterioles and larger vessels.

This is entirely favourable to the possibility of mechanical obstruction in these unmuscular smallest vessels, and the obstruction thus produced reacts on the larger muscular vessels behind and gives rise to pressure and strain and eventual degenerative change.

Some interesting points with regard to the solubility of uric acid in the blood have been published by Dr. C. Mordhorst, of Wiesbaden,

in "Die Entstehung und Auflösung der Harnsäureverbindungen ausserhalb und innerhalb des Menschlichen Körpers," *Zeitschr. fur Klin. Med.*, 32 Bd., H. 1, u. 2.

He distinguishes two forms of urate: (1) The spherical urate (which probably corresponds to the colloid urate, investigated by Mr. Saul), with a spheroidal structure under the microscope, and (2) the needle urate—the biurate or acid urate of sodium.

The spherical urate differs from the needle chiefly in its alkaline content. It does not appear to be a definite combination, but contains more or less alkali according to the quantity available in the fluid in which it is dissolved or suspended.

The more alkali and the less uric acid it contains the more soluble it is; but if with any given alkalinity the saturation point is exceeded, the urate is thrown out in minute spheres, invisible at first, but gradually combining into visible masses.

The spherical urate is thus suspended not dissolved; but the addition of a solution of sodium will bring it again into solution, or the addition of an acid or acid salt will still further throw it out of solution.

The longer the spherical urate has been in suspension the more difficult it is to redissolve it, and after some time it begins to decompose into sodium and acid urate of sodium (needle urate).

If a solution of sodium is added to crystals of uric acid, spherical urate is formed, and becomes visible in suspension round the uric acid crystals; with excess of alkali the spherical urate passes into complete solution.

The spherical urate in solution or suspension is that which occurs in the blood and tissue fluids; Mordhorst does not find in the blood any urate having less sodium than the biurate (needle urate), such as the quadriurate of the late Sir W. Roberts, though he thinks such a quadriurate may be a stage in the change from acid urate to uric acid.

A perfect gradation thus appears by addition of alkali, from uric acid, through quadriurate and acid urate up to spherical urate, and a corresponding change in the reverse direction from spherical urate to uric acid by the action of acids or acid salts reducing alkali.

Hence everything raising alkalinity increases the solubility of uric acid, and everything diminishing alkalinity diminishes its solubility, which is in complete accord with all my physiological results in the human body, as well as with the uric acid filter results.

Mordhorst obtained these results by placing uric acid or urates under the microscope, and treating them with solutions of caustic alkali, salts, or acids.

When the spherical urate is in solution its precipitation is brought about by over-saturation of the containing fluid, which may be produced either by the addition of uric acid, taking away of alkali, evaporation or cooling.

Owing to defective circulation, the fluids in the slightly vascular fibrous tissues and cartilages of joints tend (as Sir A. Garrod has already pointed out) to be less alkaline than other tissue fluids, but they contain the same quantity of spherical urate as the blood.

The spherical urate in the fluids of these tissues is likely to be thrown out, partly on account of diminished alkalinity and partly because in sedentary conditions the fluids are not moving much between and through the tissues.

This spherical urate is first thrown out in minute particles, which, however, may unite and congregate into larger masses many times the size of a white corpuscle. These increasing masses eventually block the lymphatic vessels of the part and give rise to stasis, pressure and pain, and this is, according to Mordhorst, the causation of an attack of rheumatism, with local swelling and tension.

If the spherical urate is left *in situ* the needle urate is eventually deposited; but, as in rheumatism, there comes very soon a general rise of alkalinity, the spherical urate is redissolved again without, it may be, leaving any needle urate; the needle urate can also take up alkali and pass again into the spherical form.

In gout the spherical urates remaining longer in suspension become more difficult to dissolve, and hence the needle urate is more likely to be thrown out; but it is the spherical urate which causes local irritation and tissue changes, and when the needle urate is thrown out irritation ceases.

Mordhorst also believes, in opposition to Ebstein, that necrosis of tissue is entirely secondary to the throwing out of the spherical urate, and this subject he has treated in "Zur Entstehung der Uratablagerungen bei Gicht," *Virchow's Archiv*, 148, B., 1897.

I can give but an outline of his results with the microscope, but it is obvious how favourable they are to the explanation of my physiological results. Dr. Mordhorst writes to me: "I am convinced of the correctness of your opinion, that the uric acid is retained in the tissues of the different organs through an abnormally low alkalescence"; and again: "I am of opinion that Sir William Roberts has made the mistake to believe the fluid parts of the body to be a simple solution of alkaline and neutral salts, whereas it is a solution the alkalescence of which is considerably reduced through the presence of acid salts (mono-natrium phosphate), a thing still more the case in the cartilage and tissue."

It follows from Mordhorst's results that the more alkali the phosphates of the blood and tissue fluids contain the better will they hold the spherical urate (colloid urate) in solution ; and this is in accord with what I pointed out in the *Medico-Chirurgical Transactions* (prev. ref.) that binatrium phosphate given with sodii bicarb. increases excretion of uric acid, while if the same is given with dilute phosphoric acid, or even with a salt such as sulphate of sodium, it causes no plus excretion of uric acid, but perhaps even diminished excretion.

It interests me profoundly that Dr. Mordhorst should see reason to suggest that the spherical (or colloid) urate could block the lymphatics, and thus give rise to some of the phenomena of rheumatism, for this corresponds with my suggestion that it may mechanically obstruct the blood capillaries, and thus account for the phenomena of defective circulation and high blood pressure.

Among points of minor interest, he lays stress on the influence of cold in throwing the spherical urate out of solution, and its bearing upon the causation of rheumatism locally in certain exposed tissues, and this also supports the explanation I have given of the limitation of Raynaud's disease to the skin and superficial structures of the thicker parts of limbs.

Dr. Mordhorst is a believer in the presence of uric acid in healthy blood, and thinks that von Jaksch and Klemperer, who found none, worked on too small quantities (prev. ref., p. 21 of reprint).

He believes that blood can at times dissolve more uric acid than it can hold in solution, and this is in favour of my conclusion that uric acid interferes with its own solubility in the blood, and is interesting in reference to the effects of alkalies, since they may, as I have suggested, bring much uric acid into the blood, and yet when there may fail to hold it in complete solution and so produce collæmia and high blood pressure, while some increase of alkali may redissolve the colloid or spherical urate.

He points out that the effect of deficient circulation in the skin, whether produced by cold or other causes, is to make its fluids less alkaline, so that they become supersaturated with urates, and contain the spherical urate in suspension. If this is so the defective circulation produced by collæmia will tend to perpetuate it, and hence in Raynaud's disease washing the hands in cold water may start a local collæmia, which requires a great change of general alkalinity to re-dissolve it.

I subjoin a few more facts on the relationship of urinary water to uric acid in excretion. In my notes of May 8, 1891, uric acid

was high, having a relation to urea for the whole twenty-four hours of 1 to 22. This means that there was a large excretion of uric acid, some 4½ grs. of it being washed out from deposits in the organs and tissues, and passing through the blood on its way to the kidney.

Now a large excretion of uric acid means a large excretion in the alkaline tide periods of that day.

Consider the urinary water on this day; with a large excretion of uric acid the water of seventeen hours equalled only 600 cc., or 35 cc. per hour—a very low excretion. During the seven hours of the night it was 570 cc., or 81 cc. per hour; the water retained during the day was, to a large extent, passed out when the high acidity of the night period cleared the blood of uric acid (the exact parallel of digitalis, see remarks on fig. 33).

Take another day, May 11, when the uric acid bears nearly its normal relation to urea, namely, 1 to 32; there would be but a slight excretion in the alkaline tide, and, in accordance with our premisses, little or none passing through the blood; and, under these conditions, the water for seventeen hours of the day was 1370 cc., or 80 cc. in the hour; while the excretion in seven hours of the night was 630 cc., or 90 cc. per hour. On May 8 the urine at night rose to two or three times its amount per hour in the day. On the 11th the night urine was only one eighth more per hour than that of the day; on the 8th water was retained in the day and passed out at night; and on the 11th it was passed freely in both periods. Hence, the urinary water is inversely as the uric acid excreted with it, and inversely as the amount in the blood, because the greater the amount of uric acid in the blood the more obstructed are the capillaries of the kidney.

My assertion that arterial tension (blood pressure) varies directly as the uric acid in the blood, has, therefore, other foundations besides observations of the pulse rate and tension, though these are conclusive enough. The same thing is seen when followed hourly; the urinary water is inversely as the uric acid, and if the latter is intentionally increased or diminished the water alters in the opposite direction.

This brings me to drug-action and the experimental aspect of the question, but the same laws hold good:—

(1) All substances which increase solubility of uric acid increase its excretion, and *vice versâ*.

(2) Substances which increase its solubility bring it into the blood in large quantities, obstruct the capillaries, slow the heart, and diminish the urinary water.

I have already discussed the action of drugs on uric acid: I now merely mention their effects as regards the pulse rate and tension, and the secretion of urine.

Firstly, drugs which increase the excretion of uric acid—alkalies, such as soda and potash—increase this excretion and diminish the urinary water; but as their effect on uric acid ceases (possibly because all the immediately available uric acid is cleared out) there is more or less diuresis, the water passing out which they at first retained. This is illustrated in the figures of May 8. This was a natural excretion (or fluctuation in excretion) apart from drugs, but the same thing would have occurred if I had given alkalies to increase the uric acid.

Salicylates again bring excess of uric acid into the blood, and while the excess is being passed in the urine, the water tends to be high-coloured and scanty; hence, as has been noted by several observers (Huber in *Deutsch. Archiv. für Klin. Med.*, xii., p. 129, and Stiller, *British Medical Journal*, 1890, vol. i., p. 808), the great diuresis with salicylates comes on the second day of their administration, when the excretion of uric acid and the amount of it in the blood is beginning to diminish from want of supplies.

Diuretin = Salicylate of sodium and theobromine (= dimethyl-xanthin) appears to produce diuresis in much the same way as salicylate of soda, namely, by clearing the blood of uric acid. I experimented with tabloids of this substance, and (as with salicylate of soda) there is no diuresis on the first day. On the contrary, uric acid rises and water falls. The diuresis occurs on the second or third day, when the excretion of uric acid falls. I have no doubt that the diuresis is due to the action of the salicylate element on the excretion of urates, and this explains the fact that the effects of diuretin may continue after ceasing to take the drug (Massalongo and Silvestri, "Reforma Medica," March, 1893). On the other hand, if the diuresis were due to the dimethyl-xanthin it would occur soon after administration, as is the case with uric acid, hypoxanthin, caffein, &c. (see previous remarks on these substances).

Diuretin has been said to diminish the area of cardiac dulness by exerting a tonic action on the cardiac muscle, and it is therefore proposed to give it in uræmia in place of digitalis, when there is a slow pulse (*Zeitsch. für Klin. Med.*, 1894, vol. xxii.). I have given salicylates in uræmic conditions with considerable benefit; but I doubt whether dimethyl-xanthin has any tonic action on the cardiac muscle, and I believe it reduces the area of cardiac dulness in the same way as iodides or mercury and other metals, by clearing the

blood of uric acid, freeing the capillaries and thus permitting a fall of blood pressure, which reduces resistance to its action, and, therefore, the work of the heart. Probably caffein (a relative of theobromin, which is now used as a cardiac stimulant and tonic) acts in the same way. They assist the work of a labouring heart by facilitating the passage of the blood through the capillaries, thus ensuring a general quickening of the capillary reflux, and a marked fall in blood pressure. Migraine and other high blood pressure troubles are thus relieved, whereas if the heart were strengthened without freeing the capillaries, a rise in blood pressure and increase of migraine would ensue.

With phosphate of soda the water fluctuates in accordance with uric acid excretion, and independently of the amount of the drug. When this markedly increases the excretion of acid, water tends to be low.

A large excretion under phosphate or salicylate is not accompanied by headache, but the excess of uric acid in the blood keeps the capillaries moderately obstructed and blood pressure somewhat high, though not to the same extent as if the same amount of uric acid were excreted under an alkali. This has suggested that the compound formed by uric acid with salicylates and alkaline phosphates affects the capillaries less than the combination with a simple alkali; but probably even when salicylates or phosphates are in circulation there is always some urate combined with alkali, and this may invariably account for the effect on the capillaries.

On the other hand, as is the case with alkali, complete solution may diminish collæmic effect, and absence of headache under salicylate may mean diminished collæmia, but not less uric acid in the blood.

Of drugs which diminish uric acid excretion, opium is perhaps first; I believe it acts as an acid, which in nature, apart from drugs, is the most important factor. The pulse of opium well-being and the following rebound are seen in fig. 35.

The effects of morphine in raising acidity and causing retention of uric acid are shown in fig. 15, with the quick low tension pulse, B in fig. 35; the sign of a free capillary circulation throughout the body. Its further signs are mental well-being, bodily strength, power of endurance, and a free excretion of urinary water. All these effects are due to the action of the drug on uric acid. When one morning, for example, my pulse was slow and of high tension (rate 58), I measured the urine in the hour ending 8.15 a.m., and found it 53 cc., I then took ℥ vi. of tincture of opium, in tabloids and

without fluid, the pulse at 8.15 being 62, and collected the urine of the next hour ending 9.15, no food or drink having meanwhile been taken since the previous evening. At 9.15 a.m. the pulse was 72, markedly softer, and with a larger dicrotic wave than the pulse trace at 8.15, and the urine passed in the hour was 234 cc. Obviously the comparatively scanty urine at 8.15 a.m. was not due to want of water, but to obstruction of the capillaries with which it corresponded; and the ordinary morning collæmia was ended by the action of opium as an acid.

I have mentioned mercury, and that it reduces arterial tension, and produces diuresis, the writings of Broadbent and Jandrassick testify. I believe these effects are solely due to its action on uric acid, furnishing in this respect an instance of my general laws. Fig. 34 shows the pulse tracing, A before and B during the action of

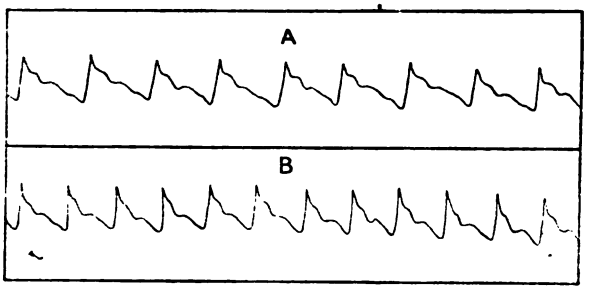

FIG. 34.—PULSE TRACINGS SHOWING THE BLOOD PRESSURE, A BEFORE AND B DURING, THE ACTION OF MERCURY.

mercury, the latter corresponding with a minus excretion of uric acid and a diuresis (see fig. 17).

Fig. 35 shows, B the pulse of opium well-being; note the quick fall, the small first wave and the relatively large dicrotic wave. The capillaries are obviously free, and the pulse soft and quick; with this urine is profuse (as in the instance mentioned above, where a dose caused marked diuresis), and there are well-being and increased mental activity.

D shows a similar pulse, produced by antipyrin; both opium and antipyrin relieve the uric acid headache.

A is the second stage action of opium, the pulse of the morning after a dose overnight. Note the slow fall, the large first wave and relatively small second wave. Headache, mental depression, malaise, disinclination for exertion occur, and the urine is scanty with excess of uric acid. The contrast between this pulse tracing and B and D is marked.

Fig. 34 shows that mercury produces a pulse like B or D, because it also clears the blood of uric acid, and cures migraine.

Lithia produces the same results. I have given, with reference to fig. 14, my explanation of the fact that it reduces excretion of uric acid.

It markedly diminishes the acidity of the urine, and yet, unlike the similarly acting alkalies, it reduces blood pressure, quickens the pulse, and produces diuresis. It is clear that the effects on blood pressure and flow of urine depend on the uric acid and not on the acidity, alkalinity, or other power of the drug. Soda and potash

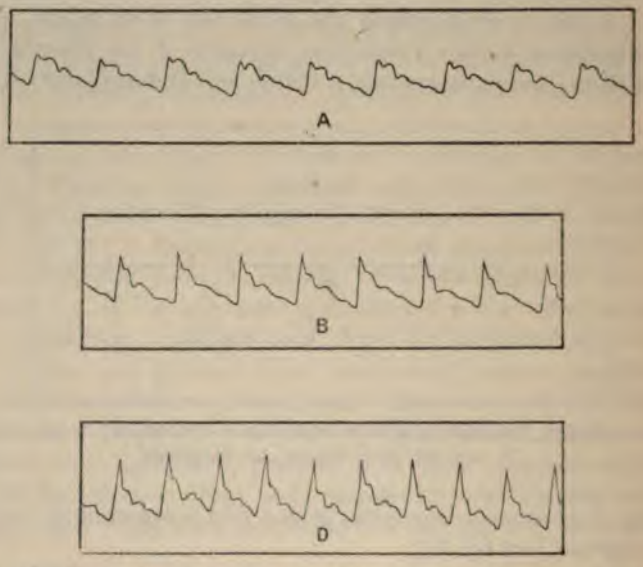

Fig 35.—Pulse Tracings of Opium Rebound, of Opium well-being and of Antipyrin well-being.

raise the blood pressure, diminish the urine and alkalise it. Lithia diminishes blood pressure, increases urine, and also alkalises it, but soda and potash increases the uric acid excretion, whilst lithia diminishes it.

If all uric acid has been removed by a course of salicylates, soda or potash will not increase uric acid excretion, and in this case they will also fail to raise blood pressure and diminish the flow of urine.

The facts about lithia are very interesting. I find that on a day when no drugs were taken the urinary water was 1280 cc., and there

was a plus excretion of uric acid (1—24). Next day 25 grs. of citrate of lithia were taken, and with this there was, as is usual, a great fall in acidity of the urine, viz., to 38 grs. from 62 grs. on the previous day, but in spite of this, uric acid was diminished greatly, having a relation to urea of 1—44. Mark the result; if an alkali had been given to produce such a fall of acidity, a plus excretion of uric acid would have resulted, blood pressure would have been high and urine scanty, but lithia, for reasons previously given, produced retention of uric acid, cleared it from the blood, and in spite of rising alkalinity free capillaries and a marked diuresis resulted. The day before the lithia, the urine containing a plus excretion of uric acid was 1280 cc., that of the lithia with a minus excretion of uric acid was 1790 cc. Here again the freedom of the capillaries and the diuresis depend not on the greater or less alkalinity, but on the greater or less amount of uric acid in the circulation, and lithia apparently prevents collæmia like an acid, by throwing a certain amount of phosphate of soda out of action. Possibly the non-appearance of these phosphates in the urine may account for the fall in its acidity.

A somewhat similar fall in acidity of the urine accompanies the diminished excretion of uric acid produced by iodides, and this suggests that the unexplained retention they produce may be the result of some effect on the phosphates of the blood, though I believe there are no known chemical facts to support this.

In contrast to lithia, note other alkalies. On March 16, 1888, no drugs, urine 1410 cc.; on March 17, pot. bicarb. gr. xxx., urine 1400 cc.; on the 18th, pot. bicarb. gr. xx., sodii bicarb. gr. xx., urine 1170 cc., and with this fall in urinary water a plus excretion of uric acid.

On May 19, 1887, with no drugs urinary water was 1670 cc., and uric acid to urea 1—32. On 20th, with 70 grs. of bicarbonate of potash urine was only 1260 cc., and uric acid to urea 1—26, *i.e.*, with a plus excretion of uric acid as the result of the alkali, the urinary water was reduced, which corresponds with the fact, that in the natural plus excretion of uric acid in migraine urine is scanty, and supports my statement that urinary water is inversely as the uric acid excreted with it.

The action of iron and lead is the same; so long as they diminish uric acid excretion they free the capillaries and produce diuresis. Afterwards uric acid is excreted in excess, and high blood pressure, slow pulse, and scanty urine occur just as in the opium rebound.

All other drugs diminishing uric acid excretion produce the same results; cocaine, antipyrin, the nitrites and various salts of the

mineral acids, especially sulphates. Strychnia also (possibly indirectly) raises acidity and affects uric acid, the pulse and urine.

Fig. 23 shows us the effect of copaiba, and we see that its diuresis corresponds with a marked fall in the excretion of uric acid, so that doubtless the capillaries were freed. I believe this is typical of a number of resinous substances, all of which probably act in the same way. Copaiba introduces a considerable quantity of copaivic acid in its resin, which forms glycuronic acid in the system, and one or both of these may affect the neutral phosphates of the blood and prevent their being good solvents of uric acid. Tar contains several acids. Rhubarb contains chrysophanic acid, and cannabis indica a resinoid substance, cannabin, which, like the resin of copaiba, may consist of acids. All these stimulate, causing free capillaries, well-being, and more or less diuresis, and these effects correspond in time with a diminished uric acid excretion. Tar is a stimulant, and in the form of a patent medicine which I have used, it undoubtedly causes marked well-being and freedom of capillaries.

It is interesting to remember its value in lung troubles, as bronchitis and phthisis, for if it acts on uric acid it will no doubt free all the capillaries and assist in lung troubles in the same way as the iodides. Tar water is, I believe, one of the constituents of Hair's Asthma Cure, in addition to an iodide, the action of which it no doubt increases.

Liquorice is another substance used in bronchitis and catarrh, and its action as a stimulant is referred to by Dr. Keith ("Fads of an Old Physician," p. 77). I have little doubt it contains some resin or acid similar to that of tar or copaiba. Its solution in distilled water distinctly reddens litmus, and this no doubt accounts for its stimulation.

Rhubarb has stimulating powers, causing freedom of capillaries and well-being, and its valuable action in gouty dyspepsia is probably due to its effect in stopping collæmia.

Cannabis indica is a still more marked instance, and its stimulation is clearly contemporaneous with a diminished uric acid excretion. Its powers are great in curing or preventing the uric acid headache; it is very useful also in melancholia, mental depression and bad temper; like tar, it is efficacious in asthma and phthisis.

Another drug with similar action, the American spirit weed (Lachnanthes), has been recommended for phthisis, and it also raises acidity and clears the blood of uric acid, causing marked well-being.

Cannabis indica has been suggested as a hæmostatic in menor-

rhagia, and this is extremely interesting, as drugs such as mercury and iodides, with the same effect that cannabis indica has on uric acid, are often very useful in hæmoptysis, when they probably act by lowering blood pressure.

Recalling the fact that clearing the blood of uric acid means freeing circulation and quickening combustion and metabolism, we shall understand how many of these drugs affect simultaneously such different organs and tissues as the skin, the brain, the lungs, the stomach, the kidneys and the uterus.

This exposes the nonsense often talked about diuretic drugs and their action on the renal epithelium. It is demonstrable that they act similarly and contemporaneously on the epithelium and cells of every gland and tissue, because they clear up collæmia and allow a free capillary circulation, hence the corresponding fall in blood pressure and the lessened diameter of the radial artery.

It is a clinical fact that rising one or more times in the night to pass urine is a common symptom in Bright's disease, but it would appear that this is more often a symptom of high blood pressure—a condition associated with Bright's disease.

I feel sure that a patient thus circumstanced has high blood pressure (apart from considerations of irritation in the urinary passages), but Bright's disease may or may not be present.

The excretion in my own person on May 8 is a sufficient illustration. On this day there was marked collæmia in the alkaline tide, and the urine during the day was only 35 cc. per hour. At night acidity rose, collæmia ceased, and the excretion of water rose to 81 cc. per hour. Something similar happens daily in the high blood pressure of Bright's disease; there is chronic collæmia, most marked in the alkaline tide of the morning, when the slow pulse is slowest, and the hourly excretion of water lowest, and the temperature in the mouth and rectum at their furthest distance apart. It is least marked in the acid tide of the night, when the pulse is quickest and the hourly excretion of water highest. Hence the patient with high blood pressure, apart from Bright's disease, is disturbed because he excretes much more water per hour at that time; and in my own case I have, under conditions similar to those of May 8, been roused up in the early hours by a distended bladder. With opposite conditions eight or nine hours may easily pass without micturition.

For a case in which the hourly excretion of urinary water was greater in the night than in the day in association with slow high tension pulse, see article on "Obesity Treated by an exclusively

'Nitrogenous Diet and copious Libations of Warm Water," by Thomas D. Savill, with remarks on the excretion of uric acid, by Alexander Haig.—*Lancet*, 1893, vol. ii., p. 133.

When the urine is scanty it is generally possible to distinguish whether this is due to concentration of the blood, or to obstruction of capillaries preventing outflow of water from it (see effects of opium previously mentioned).

When it is scanty, owing to concentration of the blood, there is no diuresis at night, the water of the night hours being as scanty as that of the day. When it is scanty during the day, owing to collæmia and retention of water in the blood, it is profuse at night, for the blood is naturally cleared of uric acid, the capillaries are free, and all the water retained during the day rushes out. This is well seen in that exaggeration of normal conditions, chronic morbus Brightii; the urine is scanty, and the blood dilute during the day, while collæmia and constant obstruction of capillaries are greatest; but urine is profuse and the blood relatively concentrated during the night, when collæmia, as in normal conditions, is less and the vessels relatively free.

If under pathological conditions the plus uric acid in the blood continues all night, as sometimes occurs in the uric acid headache, the water is scanty also; but abundant evidence exists that this is not owing to concentration of the blood in the diuresis as the headache ceases.

When the blood is concentrated, the urine is as scanty by night as by day. I give an instance:—

On 18th March I took a long bicycle ride, and being out of training I perspired greatly; the urine was 920 cc. (on the previous day 1230 cc.), = 40 cc. per hour in sixteen hours of the day, and 35 cc. per hour in eight hours of night. On the 19th it was 900 cc., 35 in the day and 42 in night. On 20th, 1030 cc., 39 in day and 50 in night, and on 21st, 1370 cc., 45 in day and 80 in night. It had now returned to nearly normal quantity, and the urine per hour at night, as is frequently the case, nearly doubled that of the day. When the blood was concentrated, the water per hour at night was less, or not greater than that in the day.

In such a case there is thirst, but when the urine is scanty, owing to collæmia and obstruction of capillaries, there is a distaste for fluids. Hence, persons who suffer from chronic collæmia and high blood pressure (as in chronic Bright's disease and conditions bordering on it), seldom experience thirst.

As for the slow high tension pulse of Bright's disease (slowest

and of highest tension in the hours when uric acid excretion is normally greatest, and quickest and of lowest tension in the nightly acid tide) we can quicken its rate and reduce its tension by any of the drugs which diminish collæmia, just as in temporary collæmia of a headache. In some cases of Bright's disease, where the pulse was slow, I have been able to nearly double its rate by influencing the uric acid, see fig. 36, where A shows a very high tension pulse, rate 52, and B, the pulse of the same patient ten days later, when the drugs had acted, rate 80. Several years ago there was some writing about the value of opium in nephritis, and in uræmic convulsions. I then tried opium in one or two cases of Bright's disease, and where the pulse was slow, it invariably quickened it and increased the urinary water. I certainly thought it did good, though in nephritis I have generally preferred to use acids or drugs (such as the iodide of mercury), which act similarly.

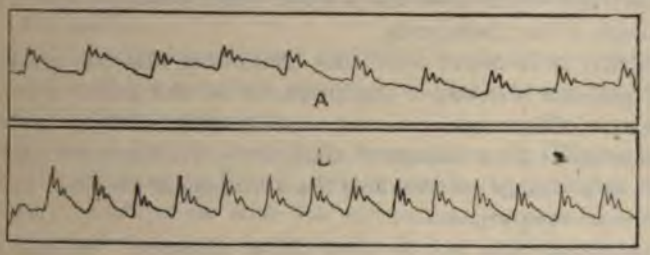

Fig. 36.—Pulse Tracings of High Blood Pressure in Bright's Disease and of the effects of drugs upon it.

It may interest those who have not a laboratory, if I say that the main characters of the high and low tension pulse can be demonstrated by means of a Higginson's syringe, a screw clamp, and a few feet of soft rubber tube large enough to fit over the nozzle of the syringe. Fill the syringe and tubes with water, and screw up the clamp so that the water can only run out very slowly from the end of the tube; adjust a sphygmograph over the tube between the syringe, which with the muscular hand outside it represents the heart, and the clamp, which represents the more or less obstructed capillaries. When all is ready set the clock-work of the sphygmograph in motion, and work the syringe regularly by the second hand of a watch. If the clamp is much screwed up, you will get a slow diastolic fall, the secondary waves being nearly obliterated. If it is so open that the water passes easily you get a quick diastolic fall with large secondary waves, as in the dicrotic pulse. If the

finger is placed over the tube instead of the sphygmograph, you will appreciate the difference between an artery full between the beats and one which is empty.

While speaking of mechanics and physics I will mention the arteriometer, invented by Dr. G. Oliver, and produced by Mr. Hawksley, the well-known instrument maker; because it is of considerable value in aiding the clinical demonstration of the effects of uric acid on the circulation.

I must only mention the most important points, and refer my readers to Dr. Oliver's work for further information.*

The arteriometer professes to measure the distance traversed by a button in passing from one side to the other of any exposed artery, that is to say, the diameter of the artery or the distance it travels in effecting its obliteration.

The fact that the artery is obliterated is recorded by the finger of the observer, which notes the point at which pulsation ceases on the distal side of the instrument.

Briefly, it is found with this instrument that the greater the blood pressure the larger the diameter of the radial artery, and though Dr. Oliver has invented another instrument for measuring pressure apart from change of diameter, since diameter practically varies with change of pressure, the arteriometer is alone sufficient for most of my purposes.

Its clinical value may be shown by an instance. We may say of a patient that his pulse was slower and of higher tension in the morning, and quicker and of lower tension in the evening; but with the arteriometer we can say that his pulse in the morning was 55, and radial diameter 2·0 millimetres, and in the evening his pulse 65, and radial diameter 1·5 millimetres.

Dr. Oliver discusses the effects of posture (sitting, lying and standing) on the calibre of the radial artery,† and has found them very constant, but I think he does not completely investigate the causes of the changes produced by posture, and certainly says nothing about the force of gravity, to which, I believe, they are really due.

On ordinary physical principles it appears that blood will travel more quickly down hill than up—will go better with gravity than against it, and the sphygmograph tells us that this is so with our circulation.

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* "Pulse-gauging," by G. Oliver, M.D., F.R.C.P. H. K. Lewis, London, 1895.

† Previous reference, p. 13.

Take, for instance, a pulse tracing, sitting or standing, with the wrist on the level of the head; gravity is here acting against the circulation, 1½ or 2 oz. pressure will be quite sufficient to develop the tracing, which will give the ordinary signs of low blood pressure.

Next take a tracing with the wrist on a level with the apex of the heart; here gravity is acting slightly with the circulation, in so far as the arteries of the arm are below the level of the aortic arch; perhaps 3½ oz. are now required to develop the tracing, which shows moderate blood pressure.

And, lastly, bending forward, sink the wrist between the knees to increase the force of gravity; it may now take 5 oz. pressure to develop the tracing, which will show high blood pressure.

Do the same with the arteriometer. With the wrist on a level with the head it will read ·5 m., on a level with the heart, 1·1 or 1·2 m., and between the knees 1·5—1·6 m. Of course the absolute diameter will vary with the person, but these are average readings on my own radial.

The changes of calibre noticed by Dr. Oliver, in different postures, are therefore simple results of the various effects of gravity on the circulation in these positions.

With the wrist at the level of the heart, or, as Dr. Oliver advises, about 2 in. or less below it, it is obvious that in the sitting or standing posture gravity acts with the circulation, because the radial artery is below the aortic arch, while in the recumbent position gravity is neutral, because the radial artery is on its level.

Hence in the recumbent position one best gets the effect of the blood pressure on the artery, but in clinical observation it is a very valuable thing to have a constant force like gravity which one can add on to blood pressure at pleasure, because this will obviously produce greater effects the less the original distention of the arteries, and vice versâ.

On the well-known principle that a candle added to the sun produces no visible effect, while a candle brought into a dark room produces much, the addition of the constant distending force gravity to a vessel with walls already greatly distended by high blood pressure, will be inappreciable; but the same force of gravity applied to a vessel whose walls are relatively lax from low pressure will produce a large distention.

Therefore the higher the blood pressure the less will be the variations induced by change of posture, and the lower the blood pressure the greater, and this is the case.

Thus the diameter of my radial artery is generally greater in

the morning and less in the evening, and the postural variations are less in the morning and greater in the evening. The following are common readings: Morning, sitting, radial diameter 1·2, lying, 1·1; evening, sitting, radial diameter 1·0, lying 0·8.

Dr. Oliver's observation is therefore comprehensible:—"As a rule as years advance beyond the middle period of life the range of postural variation becomes gradually lessened, and it may thus mark the progress of physiological arterio-sclerosis, until the calibre may at last become quite uniform in posture."

For "physiological arterio-sclerosis" I prefer to read physiological (? pathological) collæmia, and the causation of this depends simply on first principles, for every man on ordinary diet stores a large amount of uric acid, and as the decline of life begins this is dissolved and passes through his blood, causing high blood pressure, which in its turn is the cause of the gradually lessening variations in the diameter of the arteries from change of posture, in accordance with the rule worked out above.

Doubtless high blood pressure and the blocked, obstructed, vasa vasorum, are mutually the cause of the arterio-sclerosis, a pathological change which supervenes upon the physiological collæmia (see further on).

Arterio-sclerosis and its treatment have been much discussed, but I have seen nothing to prove that it is not usually due to defective circulation in the vessel walls, and to the high blood pressure and strain which uric acid produces acting with other things. Dr. W. H. Thayer and Dr. Brush write in the *Journal of the American Medical Association*, September, 1904; and one of their conclusions is that the main factor is the overstrain of the vascular wall from more or less continued high tension. No student of the uric acid problem can fail to see that infectious fever produces or conduces to such high blood pressure. The invariable effect of fever in its early stages is to store uric acid, and when the fever is past it begins to pass into the blood and causes high blood pressure, and as the effect of the collæmia so produced is to cause general malnutrition, almost all the uric acid on store may gradually pass through the blood and prolong the high blood pressure for sufficient length of time to cause more or less damage to the vascular structures.

It is part of the essence of my argument that this physiological collæmia can be controlled by altering diet, and that this accomplished, pathological effects will be diminished and postponed, chief among these effects being that gradual failure of combustion,

metabolism and nutrition, which we call chronic Bright's disease, because it is a mere prolongation or accentuation of the diminished combustion which collæmia causes. This is seen (1) in its simplest form in the fall of urea as the result of exercise in persons with plenty of uric acid available for collæmia, and in every uric acid headache there is a fall of urea corresponding with the rise of uric acid, and a rise of urea as the uric acid falls; and (2) in its most severe form in the fall of urea, and the excretion of unmetabolised albumen in its place in acute Bright's disease. In the physiological condition the removal of collæmia by mercury or its prevention by diet, suffice to prevent the fall of urea, and it is replaced by a rise; in the pathological condition the same metal, if it will act, will soon reduce the albumen to a trace and send up the urea correspondingly, increasing it by tens or even hundreds of grains.

I believe in all these conditions and intermediate conditions between migraine and morbus Brightii, the actual rate of combustion and metabolism in the body can be estimated from the rate at which a simple food (such as half a pint of milk) produces such a rise of urea as is noted in "Diet and Food," fig. 2; and the slower this rise and the less its extent the worse is the metabolism and combustion in question.

In epilepsy the pulse is often slow and of high tension just before the fits, and I suggest that high blood pressure is the actual cause of the fits. In epilepsy I have shown that this pulse corresponds with an excessive uric acid excretion and probably with more or less distinct collæmia. The urine excreted at the time of a fit is scanty, and of high specific gravity.

In uræmic convulsions I have quoted the late Sir W. H. Broadbent's opinion that the high tension causes the fits, and in writing of Bright's disease I shall point out that the blood has been proved to contain excess of uric acid, and the fact is easily explained. So that uræmic fits or the high blood pressure which produces them may be, as in ordinary epilepsy, due to uric acid.

Probably this explanation applies to puerperal convulsions, as the fits occur when some collæmia is almost certainly present (*Brit. Med. Journ.*, Feb., 1889, p. 290; also previous remarks about the effects of menstruation, pregnancy, &c.). The value of milk diet in preventing eclampsia is now very generally recognised (see Charpentier, *Sem. Méd.*, 16 Sept., 1896), which coincides with my experience, as I have had under my care a considerable number of pregnant women suffering from Bright's disease, and on a milk or uric-acid-free diet for some months before delivery they have all done perfectly well, without any sign of convulsive troubles.

In mental depression Sir W. H. Broadbent has pointed out that the pulse is often slow and of high tension, while I have shown that these conditions are often associated with an excessive uric acid excretion and more or less collæmia, and that they may be relieved or cured by controlling uric acid.

The fact on which I have laid so much stress, that the urinary water varies hourly and daily, and in physiology as well as pathology and drug action, inversely as the uric acid excreted with it, seems to me to afford irrefragable proof of the action of uric acid on the capillaries.

A dose of alkali, either in the morning before breakfast or three times a day before meals, for those who have not large stores of uric acid, will often completely prevent recurrence of headache, and watching the capillary reflux thus produced we shall understand the process. It equalises the excretion of uric acid throughout the twenty-four hours, so that there is no evening retention and no corresponding morning plus excretion; and the migraine being due for the most part to fluctuations in the excretion of uric acid, it is explicable how anything preventing these fluctuations and flattening the capillary reflux curve will help to prevent headache.

In persons with much uric acid the first effect of taking alkali may be headache, but when this ceases the equalising effect of the alkali begins, and they are more or less free from headache while it is taken.

It may not always be necessary to take alkali three times a day; a single morning dose of 30 to 40 grs. before breakfast may be sufficient.

Administration of alkali was said by the late Dr. Radcliffe to diminish the tendency to epileptic attacks, and no doubt it acts in the same way.

It is remarkable that sufferers from migraine sometimes remain free from attacks while they reside in a hot climate, this acting the part of an alkali. In an interesting letter from Dr. H. C. Dent, he says: "The one period excepted (*i.e.*, in which he had no headache) was during three years in the plains of India, and during my sojourn there I had but one attack, and that was during a short visit to a hill station." And he adds, "Evidently while I sweated freely in the plains I did not lock up any acid in excess." Here then is the cause of the periodicity of the headache, viz., periodic accumulation, we must also bear in mind the direct solvent action of heat on uric acid.

That urinary water varies inversely as uric acid, anyone who

estimates the excreta for a few days can convince himself, there is always more uric acid and less water in the morning and *vice versâ* in the evening and night, and it does so because an excess of uric acid over urea in the urine comes from an excess of uric acid in the blood, and an excess of uric acid in the blood (collæmia) obstructs the capillaries and diminishes the excretion of water, just as do digitalis and erythrophlæum; therefore obstruction of capillaries varies directly as the uric acid in the blood (Q.E.D.).

Obstruction of capillaries has no relation to any of the drugs used to affect uric acid, because these act differently in accordance with the amount of uric acid present for them to influence. Thus an alkali given to a gouty person will cause high blood pressure and severe depression; remove the uric acid beforehand with a salicylate and it will cause none. Lithia produces no depression and allows a free flow of urine; soda and potash cause depression and scanty urine; all render the blood more alkaline and the urine less acid; but lithia clears the blood of uric acid, while soda and potash produce collæmia.

A side light has been thrown on this subject by Romberg, who says (*Therapie d. Gegenwart*, May, 1904, page 221) that the viscosity of the blood may be diminished by as much as 10 per cent. by the administration of potassium iodide. The action of potassium iodide is to diminish the uric acid in the blood and urine, and hence it is the drug which I most frequently administer to keep down blood pressure in conditions of collæmia; nor is it necessary to keep to potassium iodide, for iodide of sodium or iodide of mercury are as good, or better. Probably this so-called viscosity is often another word for collæmia, and with the same causation, though I am aware that viscosity is greatly increased in polycythæmia, but this is a somewhat rare condition, and if increase of uric acid increases viscosity great increase of cells may do the same. I can answer for it that blood cleared of uric acid will at once circulate more freely in the capillaries, and this without any regard to the method used, the rate of the capillary circulation being invariably a measure of the amount of uric acid in the blood.

Other writers state that purin bodies contract the arterioles, and thus raise blood pressure. I believe that in high blood pressure the arterioles are, like the arteries, not contracted, but dilated, and that the only obstruction in the circulation accounting for all observed results must be in the capillaries. (See also my paper on "Capillary Circulation and Blood Pressure," *Medico-Chirurgical Transactions*, 1906). These supporters of the purin theory offer no explanation of

the way in which these bodies contract the arterioles, whilst uric acid is undeniably present in the blood, and the amount of obstruction it produces in the capillaries can be easily measured.

Sir W. H. Broadbent points out in the *Lancet* (vol. i., 1905, page 1401), that he places the resistance to the circulation in the capillaries. He attributes the resistance to blood impurities, and draws attention to Dr. Oliver's interesting remark that boiled meat raises the arterial tension less than roast meat, failing, however, to realise that the impurity is uric acid, which, by the mechanical action of its colloid form, obstructs the capillaries. Nor does he add the simple explanation of Dr. Oliver's remark, viz., that boiling extracts more of the uric acid than roasting, hence boiled meat raises the blood pressure less than roast. Sir W. H. Broadbent calls attention to the fact that a single grain of calomel or pil. hydrarg. produces a striking reduction of arterial tension, but here again omits what I have stated for years, that mercury clears the blood of uric acid, quickening the capillary circulation and lowering the blood pressure by doing so.

Dr. Oliver, *Lancet*, 1903, vol. ii., page 945, remarks that, "when gout becomes acute, the embarrassment of the peripheral circulation which characterises the chronic form of the disease suddenly vanishes, and the fall of the capillary blood pressure which ensues suffices to secure complete absorption of the pent up tissue fluid." In this extremely interesting passage he confirms my observation on the causation of dropsy. For when gout becomes acute the capillary circulation is cleared from the obstructing influences of uric acid, and diaphoresis, diuresis, and the free passage of fluid from the tissues naturally ensue. The causation of dropsy reverses this, and the retention of fluid in the tissues is caused by the obstructing influence of colloid uric acid both in the capillaries and the interstices of the tissues.

A paper has been published by Dr. Nathan Rosewater in the *New York Medical Journal*, July, 1905, under the title "A Case of Lithæmic Gangrene, a Contribution to Haig's Uric Acid Theory."

This patient had several superficial gangrenous ulcers, and Dr. Rosewater put him on uric-acid-free diet, and gave salicylate of soda and other drugs. In due time the ulcers disappeared; about two months later he came with a violent skin irritation, and acknowledged that he had broken rule and eaten a steak, which, he declared, "was hardly down three hours when this awful itching came." Three months later he returned with a localised gangrene in the right foot. Subsequent investigation revealed that his wife had been

giving him beef tea twice a day for a month. In the treatment of the case Dr. Rosewater mentions that the patient (who was sixty-four years of age) became delirious when digitalis was given, but delirium ceased when the drug was withdrawn. With reference to this matter he refers to Dr. Hall, who points out that digitalis often produces this effect in the senile. At first sight it seems extraordinary that a drug such as digitalis, which raises the blood pressure, should produce a condition generally associated with low blood pressure; but the explanation probably is that digitalis obstructs the local circulation, and that the power of the heart in a senile patient cannot overcome this obstruction; hence defective circulation in the cortex of the brain and resulting delirium. A similar defective circulation in the cortex is the cause of delirium in the low blood pressure conditions with which it is more frequently associated.

After recovery from the gangrene, the patient did well for nearly a year. Some relapse of asthma and insomnia then occurred, and it was discovered that he had to some extent returned to tea and coffee. These being stopped, he remained well for more than seventeen months.

Much of the paper is devoted to discussing the uric acid theory. The writer lays stress on the observation of Romberg. He points out that endogenous uric acid is uninfluenced in a normal organism by the general metabolism, and proceeds to point out that those who hold endogenous uric acid to be at fault in gout, are illogical in considering diet, though diet for gout is almost invariably attempted.

I have said that the obstruction of the capillaries varies directly as the uric acid in the blood, and pulse rate according to Marey varies inversely as arterial tension, which is the result of capillary obstruction; therefore, pulse rate varies inversely as the uric acid in the blood.

This opens a subject about which much has been written, namely, bradycardia, or slow action of the heart. Prof. Reigel divides bradycardia into physiological and pathological; and a close investigation shows that in all his conditions there is collæmia obstructing the capillaries; and the bradycardia is due to this, in accordance with Marey's law.

In the physiological group come (1) the bradycardia of ten to twelve days after confinement; (2) that of conditions of hunger; (3) that of individual peculiarity.

After confinement, as I have pointed out elsewhere (*British Medical Journal*, Feb. and Nov., 1889), there is almost certain to

be collæmia, because there is an interruption of digestive and other functions at the end of a period of active nitrogenous metabolism (pregnancy). These facts probably give the causation of puerperal convulsions.

In certain conditions of hunger, also, there is a fall of acidity and temporary collæmia.

As to individual peculiarity, Prof. Reigel suggests that it often means unrecognised disease.

In the pathological group comes bradycardia associated with :—

(1) Convalescence from acute disease.
(2) Diseases of digestive organs.
(3) ,, respiratory ,,
(4) ,, circulatory ,,
(5) ,, urinary ,,
(6) Intoxications.
(7) Diseases of blood and general nutrition.
(8) ,, the nervous system.
(9) Other diseases.

Of (1) acute diseases and their causation of collæmia I shall often speak (see chapter viii.), but meanwhile I have no doubt that the free capillaries and dicrotic pulse of fever are due to rising acidity and the consequent clearing of the blood from uric acid. The pulse of fever often resembles that produced by the nitrites, the probable causation being in both cases a rise of acidity, but a rise of acidity clearing the blood of uric acid causes retention of uric acid, and this retention will be followed (as in the case of opium and other drugs) by a plus excretion. Therefore, as fever ends and acidity falls, the retained uric acid will be dissolved and flood the blood, we shall have more or less severe collæmia according to the amount retained, and slow high tension pulse (post-febrile bradycardia), subnormal temperature, &c., in proportion. Knowledge of the effects of uric acid thus explains pulse conditions in fever and convalescence, and demonstrates that the pulse of the latter is the necessary sequence of that of the former (see p. 26).

Of changes in the rate and rhythm of the heart, Marey says that while they are often attributed to nervous influences, they are in not a few cases really due to pressure change in the vessels either of the systemic or the pulmonary circulation (prev. ref., p. 484).

Writers on post-febrile bradycardia have observed that it often attacks severely those who before the fever were strong and healthy, and yet, in apparent contradiction, they attribute it to weakness of the heart muscle.

Why should such patients have the weakest hearts after a fever? There is no doubt, however, that they would have the largest nitrogenous metabolism both before and during the fever; they would, therefore, store most uric acid and the most severe collæmia would follow the bradycardia, being doubtless in proportion to this.

As regards the heart, the only necessity for the production of bradycardia is that it shall be sufficiently strong to withstand the strain which collæmia, obstructed capillaries, and high blood pressure impose, and this is much more likely to be met with in persons previously strong and robust. If the heart fails before the high blood pressure, we shall get palpitation, or a quick, irregular pulse in place of a slow one, and some cases of tachycardia are no doubt thus accounted for; in such cases the importance of giving drugs such as morphine or mercury, that lower blood pressure, should be borne in mind, and as the pressure falls the heart will slow towards the normal rate (see also effects of chloroform and nitrites in chapter viii.). A very interesting case was mentioned at a meeting of the Clinical Society (*British Medical Journal*, 1897, vol. i., p. 144), where paroxysmal tachycardia came in sudden attacks in a child and was associated with enlargement of the heart. And the possible relations between such a condition and that of Graves' disease are most interesting. I earnestly caution those who wish to arrive at the truth not to attribute either bradycardia or tachycardia too readily to any nerves or ganglia, or to refer the benefit obtained from such drugs as valerianate of zinc or morphine to their action on those ganglia, till the presence of collæmic high blood pressure, and the possibility that these drugs have cured by relieving it, have been considered.

For an account of some cardiac cases cured or relieved by morphine, see paper by Dr. F. S. Toogood, *Lancet*, 1898, vol. ii., p. 1393.

The causation of bradycardia and tachycardia is of interest, and my belief is that both may be organic and due to changes in the nerves, vessels, or heart muscle.

But apart from such organic changes, the common cause of functional bradycardia is high blood pressure. If this blood pressure rises higher the heart may first falter and flutter, as seen in fig. 37, and finally palpitate (= functional tachycardia).

On the other hand, the heart may palpitate when surprised, so to speak, by a sudden fall of blood pressure.

The natural thing for the heart to do is to quicken as the pressure falls; a sudden fall acting on a perhaps imperfectly nourished heart may cause excessive quickening.

And this may account for several cases I have seen where palpitation has been over and over again relieved by a good dose (grs. xxx.-xl.) of sodii bicarb.

Possibly this had relieved some dyspeptic condition interfering mechanically with the action of the heart; but we must not lose sight of the fact that it would increase collæmia and raise blood pressure, which should slow the heart.

Probably the effects of blood pressure pure and simple are seen in the fact that palpitation is sometimes relieved by a few deep breaths; this undoubtedly lowers blood pressure, as it relieves the high blood pressure headache.

Some palpitation may also be stopped by holding a deep breath and pressing forward so as to compress the diaphragm with the abdomen and thighs; now this undoubtedly raises blood pressure and makes a migraine worse (see *Lancet*, vol. i., 1902, p. 1318.)

I think we have probably two causes for functional tachycardia: (1) rising blood pressure with more or less heart failure, as in Graves' disease, and (2) a sudden fall of blood pressure such as a nitrite produces (*e.g.*, a tabloid of trinitrine) or a glass of an acid wine such as champagne.

On the other hand, tachycardia due to high and rising blood pressure would probably be relieved by a nitrite or a glass of wine; and I have often seen one of these terminate such irregularities as are shown in fig. 37.

We must give these drugs, which lower blood pressure by retaining uric acid and clearing it out of the blood, with great caution, and must never forget that to leave them off suddenly is often most dangerous; for the stored uric acid at once rushes back into the blood, the blood pressure rises quickly to dangerous heights, and again heart failure or cerebral hæmorrhage may result.

I have seen several such cases after discontinuing iodides or morphine, and have heard of many more, whilst the dire effects of suddenly leaving off an opium-eater's dose are familiar; but in all these cases considerable safety may be attained by giving a short course of salicylates before stopping the retentive drug, and this plan I now follow.

(2) Digestive disturbance generally entails a fall of urea and acidity and collæmia results, which is the common occasioning cause of the uric acid headache, also of fits, mental depression, fatigue, asthma, glycosuria, anæmia, and albuminuria. All these are frequently associated with dyspepsia or gastro-intestinal upset, because they cause the collæmia. But the latter tends to make the dyspepsia worse or to continue it.

(3) Respiratory disease may entail deficient oxidation, which means a fall of acidity and consequent collæmia. Later we shall see the marked effect of dyspnœa on the capillary reflux and the blood pressure.

(4) Circulatory disease may obviously cause collæmia in several ways, for instance, by producing dyspepsia or cyanosis.

(5) Among the urinary diseases mentioned by Prof. Reigel, nephritis bulks largely, and of this and its collæmia I shall speak in chapter xiii.

(6) Intoxication by lead, alcohol, digitalis, and bile are specially mentioned; the action of lead and alcohol on uric acid I need not repeat. Digitalis acts in accordance with the same law, and slows the pulse by contracting the arterioles and raising blood pressure. The digestive disturbances accompanying jaundice probably account for collæmia, and jaundice is not always accompanied by a slow pulse, which points to indirect action.

(7) I shall only mention anæmia or leucocythæmia in reference to what I say in chapter xii. of the correlated collæmia.

(8) As regards the nervous system, I admit that certain central or reflex irritation may contract the peripheral arterioles, raise blood pressure, and produce bradycardia, but I believe that disease of the nervous system often acts indirectly by producing nausea, vomiting, or gastric disturbance, with secondary collæmia and capillary obstruction and its resultant bradycardia (see previous remarks and quotation from Marey).

Under (9) are grouped fatigue, sunstroke, severe pains in various organs, and if necessary I could prove that these may be accompanied by collæmia. I shall speak of fatigue in connection with the causation of mental depression, chapter viii.

Severe pain, especially when connected with any of the abdominal or pelvic organs, causes more or less complete arrest of digestion and absorption of food; it thus produces increased alkalinity of the blood, and collæmia, like any other digestive disturbance; but whether this accounts for the effects of all pain, fright, &c., in producing shock and collæmia I am not prepared to say. Certainly in many of these conditions much good may be done by clearing the blood of uric acid, and I have mentioned a case in which this was achieved by the natives of Morocco by means of a dose of urine. Pain has also probably a direct effect in raising blood pressure, and this would not be hindered by acting on uric acid either with drugs or diet.

As regards fatigue, since drugs such as morphine, cocaine,

acids, &c., which clear the blood of uric acid and promote a free circulation in the nervous and muscular tissues, produce (as they are well known to do) feelings of mental well-being and bodily strength, and greatly increase the powers of endurance, it is extremely likely that drugs and physiological or pathological conditions, which increase uric acid in the blood, and so hinder the circulation through these tissues, will produce potential or actual fatigue.

In connection with sunstroke, we may remember that external heat produces collæmia (see remarks on fig. 4), and that some of the symptoms of this trouble may be due to high blood pressure and others to defective combustion, in a word, fatigue with special variations (see chapter viii.).

From the causation of bradycardia by uric acid I pass to that of angina (see chapter xiv.), and of syncope (see also *Brain*, Spring Number, 1891, p. 88). Acute dilatation of the heart and other effects of high blood pressure, and the value of nitrites and mercury in such conditions, are easily accounted for. I give here, fig. 37, a tracing showing an intermission in my own pulse, when the heart was labouring against the high blood pressure of collæmia, and I suggest that epilepsy may in some cases be due to heart failure from this cause.

It must be remembered that chronic under-feeding and deficiency of food may lead to collapse and heart failure. I have seen several such cases among those who have broken my rules of quantity. The patient either suddenly collapses or gradually finds himself weak and unfit for exertion, even customary exercise causing palpitation. We find the pulse unduly quick, the first sound of the heart long or reduplicated, the heart dulness is increased, and the capillary reflux falls out of its normal relation to blood pressure. A capillary reflux of seven or eight occurs, and where we should expect a blood pressure of 140 mm. of mercury or above we find one of 100 or 110. If the heart were strong pressure should be 140, and the difference between these figures gives a measure of the extent of the heart failure.

From such a condition with care and rest the patient will recover, but not without sufficient food albumens.

Such heart failure is specially likely to be met with in those who under feed on first changing diet, for here there is certain to be more or less collæmia, which throws additional strain on the heart.

An interesting form of syncope is that which occurs during bathing, and it no doubt accounts for the loss of many lives.

Bathing is common during the morning just at the hours of

physiological collæmia, and when to this is added contraction of all the surface vessels by cold, and, as we can now understand, some increase of the urate precipitation itself by cold, it is little wonder that the heart is sometimes overpowered. It is acknowledged by Sir W. H. Broadbent ("Pulse," p. 153), that powerful contraction of arterioles may bring the heart to a dead stop. Or a patient may become sleepy with headache or even a threatening of coma under similar conditions, and these are doubtless results of rising intracranial pressure, for I have often found that a morning cold bath raises blood pressure and increases a headache if present, whilst warmth would lower blood pressure and remove headache. All sufferers from migraine should beware of cold bathing in the early morning, or they may lose their lives either from heart failure or high intracranial pressure and coma, according as the heart fails or does not fail before the rising pressure of increasing capillary obstruction.

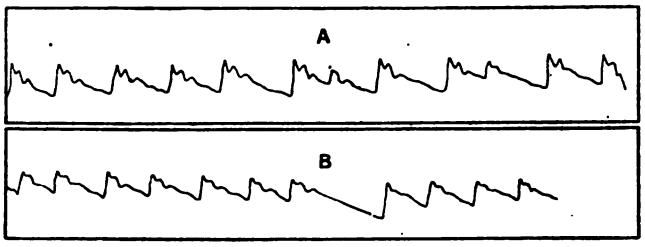

FIG. 37.—PULSE TRACINGS OF HIGH BLOOD PRESSURE. (A) FALTERING. (B) INTERMITTENT.

As regards my own pulse, I look upon a fluttering, imperfect systole, or a dropped beat, as in fig. 37, as conclusive evidence of high blood pressure. I have many hundred tracings of such a pulse, but none without accompanying (causative) high blood pressure, and I have often produced this condition or removed it in myself and others.

It is interesting to notice that Marey says the pulse in typhoid fever is, first of all, soft and dicrotic, and later, on the approach of convalescence, shows more or less high tension, and he goes on, "L'apparition du triple rebondissement [= W pulse of high tension as in trace A, fig. 37] est un caractère important de l'approche de la convalescence; nous le recontrerons à la fin des autres maladies fébriles. Au moment de la convalescence le pouls présente parfois aussi un peu d'irrégularité" (prev. ref., p. 569). That is to say, during high fever there is retention of uric acid, and little or none

in the blood, but as temperature drops, the alkalinity of the blood increases, it dissolves a considerable quantity of uric acid which obstructs the capillaries and produces high blood pressure, and the heart flutters or falters as the pressure rises.

Dr. Chapman, in his lectures on the "Physics of the Circulation," says that when the heart gives a tumble or flutter it really makes two contractions, as an effort at compensation (*Lancet*, 1894, vol. i., p. 661).

Again, with regard to alcohol, Marey says, "Certains agents, l'alcool, par exemple, mettent la circulation dans un état analogue à celui de la fièvre typhoide; le pouls de l'ivresse à moins qu'elle ne soit accompagnée de troubles gastriques présente à un haut degré le dicrotisme" (prev. ref., p. 569). Why this exception in the case of gastric troubles? Marey appears to attribute it to irritation of the abdominal sympathetic, but I am only following his own rule with regard to heart rhythm in suggesting that the absence of dicrotism in gastric trouble is really due to uric acid, and to the intra-vascular pressure changes it produces, and not directly to the nervous system. Gastric upset means diminished absorption of alcohol, and of the acids so frequently ingested with it, diminished absorption also of food with its resulting diminished formation of urea and acids, and the result is an increase in the alkalinity of the blood, which at once takes up an increased quantity of uric acid, obstructing the vessels and preventing more or less completely the dicrotism otherwise produced by alcohol and acids.

Marey adds that vomiting produces coldness of surface and extremities, in fact, all the signs of vascular contraction; he says also that John Hunter was struck by the coincidence of lowered temperature with vomiting, and concluded that the stomach was probably the seat of heat formation. Marey corrects Hunter by referring to present knowledge of the abdominal sympathetic and its supposed power of contracting the vessels all over the body, but he is probably himself quite as far from the truth.

I believe that in all gastro-intestinal disturbance, whether culminating in vomiting or not, there is a diminished formation of urea and acids (one has only to watch the effects of dyspepsia on the excretion of urea for a few days for certainty on this point), and consequently an increase in alkalinity of the blood; as a result it is flooded with uric acid. Deficient circulation throughout the body, and especially, as we have seen, in the skin, results. Even in physiological conditions the temperature of the body is largely dependent on the quantity of uric acid in the blood (fig. 5), but from the vaso-

motor or abdominal sympathetic point of view it must be shown that these centres were more active in the contraction of vessels in the a.m. hours daily than in the p.m. hours.

Some deficient circulation or vascular obstruction is the central symptom of every migraine in which the initial lesion is almost always some gastro-intestinal disturbance, though this is sometimes itself secondary to collæmia otherwise produced, as in fatigue (see chapter viii.); but when the gastro-intestinal disturbance is present it affects the alkalinity of the blood and produces or intensifies the collæmia to which everything else is secondary.

If the deficient circulation throughout the body in migraine is due to the abdominal sympathetic, why does clearing the blood and urine of uric acid control it? Why does increasing the uric acid in the body and blood intensify it?

It is easy to refer every ill-understood phenomenon to the irresponsible action of the abdominal sympathetic or the vaso-motor centre, but no reason is given why these centres should contract all the arterioles in the body because the stomach has had a slight disagreement with a pork chop. Migraine itself was considered a neurosis till I showed that the nerve centres might be neglected if the uric acid was controlled; and the obstruction of vessels in this and similar conditions is not nearly so sudden as Marey supposes, for long before the stomach trouble causes vomiting, there is more or less complete suspension of digestion and absorption; and meanwhile urea has been falling and the alkalinity of the blood and the consequent collæmia increasing. Marey sees the final stage of the process, and looks upon the obstruction of vessels as sudden, but in migraine there is often great obstruction of vessels without any vomiting.

I do not deny that irritation of a sensory nerve may cause contraction of vessels and a rise of blood pressure, but this may be due to contraction of the relatively large vessels, and is often temporary, differing in many ways from the steady and continuous high blood pressure accompanying excess of uric acid in the blood (see also case recorded in chapter viii. in connection with the causation of chloroform syncope, and other instances of the direct effects of pain mentioned later).

In migraine, where the pressure remains high for hours or possibly for one to two days, the only pain is in the head, and though there may be occasionally some nausea, there is no abdominal pain sufficient to account for irritation of the sympathetic.

Again, in physiological conditions what source of vaso-motor irrita-

tion exists in the a.m. and early p.m. hours which is absent in the later p.m. hours, or why does a dose of calomel, any acid, or the mere inhalation of ammonia, affect the blood pressure at any time? There is no reason to think that these will remove a source of gastric irritation, still less an organic lesion or scar.

Still more in pathology, *e.g.*, in chronic Bright's disease, when the blood pressure is high for days, weeks, months, and years, does its remarkable relationship to uric acid appear; clear the blood of uric acid by means of mercury, or observe its clearance by an intercurrent febrile disturbance, and the high pressure vanishes in a comparatively few minutes and is absent till the mercury or fever are gone, but no longer.

In these physiological conditions the high pressure is not due to the contraction of the larger arteries, because the arteriometer tells us that the diameter of the radial increases with the pressure; and, though these large vessels are exercising some pressure on the blood within them, this is with the object of helping the heart and forcing the circulation through the obstructions in front. Obviously, as the large vessels are dilated the rising pressure cannot be due to their action.

Applying this to all the arteries that have obvious muscular tissue, and considering that they aid the heart by a certain amount of contraction to force the blood through the obstruction in front, and that they with the heart become hypertrophied in the process, then obviously the small vessels (arterioles) nearest to that obstruction will have most pressure to bear, and may become most hypertrophied, just as the small pipe near a tap is subjected to the greatest strain when the stream is suddenly stopped.

From one point of view then, we see one nerve centre in physiological and pathological conditions engaged in aiding the heart and arteries in forcing the blood forward, while another is contracting the arterioles and keeping it back, and that internecine warfare persists for days, weeks, months and years, to the detriment of the physiology and nutrition of the body.

Is there any other parallel to this in the physiology of the human body? Is there anything in the theory of evolution to render such a belief possible?

My observation on the constant relationship of these conditions of high blood pressure, both in physiology and pathology, to excess of uric acid in the blood is the key, and we must suppose that the uric acid irritates the second centre, and sets it against the first, for the moment uric acid is removed the strife ceases.

If, however, it should eventually prove that the connection between uricacidæmia and high blood pressure is mechanical and due to blocking of capillaries by colloid uric acid, we are relieved from the belief in physiological suicide, and can realise that the physiological resources of the body are united in one common endeavour to prevent this mechanical obstruction from injuring the nutrition and functions of its tissues.

However this may be, one fact is, I believe, certain, that in physiology and pathology high blood pressure is absolutely dependent on the amount of uric acid in the blood, and that if we remove the uric acid we shall lower blood pressure, and improve circulation through every organ and tissue, and this without the least regard to any nerve centre.

Marey also points out that a feeble pulse becoming almost imperceptible in the radial, but presenting the pulse tracing of extremely high tension, is the pulse of *mal de mer*, and of nausea or vomiting. In sea-sickness there is commonly a headache, which has all the characters of the ordinary bilious headache (migraine) produced by uric acid. I see no reason to doubt that the high tension pulse is produced by uric acid, and that the headache represents the effects of the high blood pressure on the intra-cranial circulation; a similar headache can be produced in any one subject to it by anything which will produce gastric disturbance, provided a supply of urate is present which can be taken up by the blood. In accordance with this is the fact that the uric-acid-free diet relieves or even prevents sea-sickness.

Where there is obstruction of capillaries, but the heart is powerful, or perhaps hypertrophied, and refuses either to give way, dilate or furnish imperfect systoles, blood pressure will rise dangerously, and (especially where the vessels are already degenerate) hæmorrhage will occur.

This may be harmless in the form of epistaxis or hæmoptysis (and I have elsewhere* suggested that what the late Sir Andrew Clark denominated "arthritic hæmoptysis" may be due to collæmia and its effects on the circulation), or may be fatal and deadly as hæmorrhage in the brain.

I am collecting records of syncope, hæmorrhage, &c., to discover whether a majority occur at the times of physiological collæmia (*i.e.*, the "alkaline tides" of the morning or afternoon and collæmic seasons of spring and summer), pathological exaggerations of which

* Wood's *Medical and Surgical Monographs*, February, 1890, p. 359.

may account for these symptoms; and the extent to which my records favour this is remarkable.

As to the arteries themselves, high blood pressure means a certain amount of strain, and strain leads to degeneration of structure. As the vasa vasorum are affected by the urate, nutrition is involved, and degeneration, atheroma and other changes result. Hence in diabetes, a disease associated with high blood pressure (as pointed out in chapter xiv.), we get arterio-sclerosis and gangrene (see *British Medical Journal*, Epitome, 1896, vol. ii., p. 17).

In a recent (6th) edition of "Diet and Food," p. 83, I quote from "Human Physiology," by Raymond (London, W. B. Saunders, p. 128), some remarks by a vegetarian doctor on arterial degeneration as caused by his diet. He does not, however, state whether his diet includes such poisons as the pulses, tea and coffee, mushrooms, asparagus, &c., and it is therefore impossible to draw any useful conclusion.

Education and subsequent experience have taught me that the one great cause of arterial degeneration is pressure and strain. For we find degenerate vessels in those who have had high blood pressure in life, and the longer they have been exposed to this the more advanced are the changes.

They are also more marked in those who, in addition to high blood pressure, have been exposed by occupation to vascular strain, *e.g.*, by lifting heavy weights.

Again, when some vessels have been more exposed to strain than others, the degeneration is there most marked.

And though most degeneration occurs in the old owing to the greater duration of pressure and strain, fairly marked changes are found in the vessels of high blood pressure cases (*e.g.*, Bright's disease) even under the age of 25.

Thus everything, both clinically and in the *post-mortem* room, denotes that pressure and strain are the most important causes of arterial degeneration, followed and aided to some extent, and in certain cases, by such contributing causes as alcohol and syphilis.

The chief cause of pressure and strain, apart from mechanical conditions mentioned above, is high blood pressure—(uric acid collæmia, and its results)—hence the early and marked presence of such degeneration in cases of Bright's disease. It is chiefly in company with chronic Bright's disease that we find the most advanced arterial degeneration of later life.

The uric-acid-producing poisons in many vegetarian foods account for the results cited by the doctor quoted in "Diet and Food." This

accords with my experience, for some of the highest blood pressures I have ever measured, accompanied by more or less marked signs of vascular degeneration, have been in pulse-eating natives of India—a fact which accounts for many vegetarian failures nearer home.

The same observer suggests that vegetarian foods cause chalky degeneration of arteries by introducing excess of salts.

The ultimate appeal is not to theory, but to fact. Do those who live on bread stuffs and other uric-acid-free foods get high blood pressure and vascular degeneration, or do they not? So far as my experience goes the answer is in the negative.

It can be no surprise to me to learn that vegetarians who eat pulses and drink tea suffer from high blood pressure, vascular degeneration, calcification, &c. The value of this observer's testimony depends upon whether his diet was uric acid free or the reverse.

To return, the same argument applies to the effects of high blood pressure on the heart. We get first hypertrophy and then degeneration, or sudden syncope or angina occurring in the alkaline tide, due to obstruction of capillaries for which it is unprepared, the fluttering heart of uric acid headache or epilepsy being a minor stage of the same thing. Syncope and angina are treated in chapters viii. and xiv., but their causation by the obstructed capillaries of collæmia follows directly from what I have said about fig. 37, and this explains their occurrence after fevers, influenza, &c., or in association with gout, dyspepsia, Bright's disease and glycosuria; it also explains the relief afforded by mercury, morphine and the nitrites. Several of my epileptic patients tell me that they shiver with cold (obstruction of the capillaries of the skin) or feel a fluttering in their throat (sign of a single non-habitual intermission of the heart) just before a fit occurs; and the so-called globus hystericus may be a phenomenon with similar origin.

As to the skin, there is the cold skin of migraine passing through all stages to Raynaud's disease, or various interferences with function and nutrition, producing urticaria, erythema, &c., and, where the skin has long been deteriorated by urates, leading to the atrophy and loss of structure described by Semmola (see chapter xiii.) as present in Bright's disease.

In Raynaud's disease there is clearly some difficulty in believing that a spasmodic contraction of living tissues should last so long as to produce death of the parts, and Raynaud has shown (see chapter xi.) that the obstruction is not in the arteries nor veins, but in the capillaries. But if the obstruction is due to colloid uric acid, we can

see that the cooling of the blood in the exposed skin and extremities of the fingers may increase precipitation of uric acid, just as it does in the test tube, and thus the local obstruction will not only be increased, but there will be no limit to its duration, which explains the remarkable way in which Raynaud's disease is limited to surfaces and extremities. Such limitation is very difficult to explain by reference to an irritated nerve centre (see chapter xi., remarks on Dr. Southey's case).

In the brain we have, as the effect of urates on its circulation, stasis, as in headache, vertigo, epilepsy, mental depression, and œdema as in uræmia, not to mention softening and hæmorrhage from organic arterial changes.

No doubt we have in the cord similar functional and nutritional changes, and in the peripheral nerves, neuritis and perineuritis, each and all due to vascular conditions produced by urates (see Charcot in *Prog. Méd.*, vol. ii., 1890, p. 83-102, and Buzzard, *Lancet*, vol. ii., 1893, p. 1233). Toxic neuritis may represent the effects of the drug on urates. There are also many interesting eye symptoms more or less closely related to high blood pressure; for not only has stasis or thrombosis in the vessels of the retina been seen during attacks of migraine (see *Ophthalmic Review*, March, 1890, paper by Mr. Stanford Morton), but Sir T. Lauder Brunton (*British Medical Journal*, 1892, vol. i., p. 7), the late Dr. J. Anderson and others, have noticed the connection between intraocular tension and high blood pressure.

In the eye, we have probably a similar set of forces to those causing stasis and hyperæmia in the cranial circulation, and the pathology of glaucoma may closely parallel that of headache or mental depression (*i.e.*, the effect of high blood pressure in a more or less closed cavity). I have seen cases in which eye pain, apparently related to glaucoma, was immediately relieved by a drug reducing blood pressure. A patient under my care had blood pressure reduced from 180 to 110, with simultaneous reduction of tension in the eye and improvement in its condition. I have spoken of the kidneys and the way in which urates diminish excretion of water and retain it in the body, one result being probably the œdema of eyelids noticed by several observers as occurring in migraine. The late Dr. Gogarty, of Canterbury, drew my attention to it (see also *British Medical Journal*, 1888, vol. i., p. 1006, and compare anasarca case in chapter xiii.).

No doubt nutrition of the kidneys, liver, and other organs is eventually affected by the vascular changes which urates bring about in their parenchyma; the chief being an alternation of anæmia with

hyperæmia, often intensified by the serious secondary effects of collæmia on the heart and general circulation.

The muscles can scarcely suffer less than the skin and other organs, and, when their vessels are obstructed, no doubt their nutrition is seriously hindered (see the causation of fatigue, chapter viii.); and as they, like the liver, are important organs of metabolism, there can be little doubt that general nutritional changes may be induced when their circulation is impeded. I suggest that in glycosuria and albuminuria, when temporary and not associated with actual kidney lesion, we see results of such metabolic disturbance. When blood pressure is high, and is lowered by giving an acid, there is certain to be a rise of urea; and this rise of urea is due to an increased formation of urea, when the metabolic processes in the liver, muscles, &c., are set free from the restrainiug influence of collæmia. We shall see this to a much more marked extent in chapter viii., where it will appear that the amount of uric acid in the blood not only controls the amount of fatigue which a given exertion will produce, but also its effects on the formation and excretion of urea.

The late Dr. King Chambers regarded vascular tension as due to the presence of waste products in the blood, and treated the condition by diet; he took a great interest in the early stages of my research, and wrote me several letters containing points of interest; among others he mentioned a case of epilepsy, which rather to his surprise was apparently cured by diet. Dr. Chambers ordered his patient to reduce his meat and beer, but he being young and enthusiastic went beyond his instructions, and left off both entirely; eighteen years afterwards he had never had another fit; I shall have to relate a somewhat similar case in chapter vii. The step from the general belief that high blood pressure is due to waste products in the blood to the special belief that it is due to uric acid, is in some respects a small one; but it will presently be seen that in the power it gives us to control high blood pressure and its effects, it is really a very large one.

It may be both interesting and useful to restate shortly, in the form of conclusions, some of the points and arguments touched upon in the preceding pages, thus:—

The daily, hourly, and seasonal variations in blood pressure are practically inexplicable if uric acid fluctuations do not cause them. So are also the well-attested effects of milk diet or other uric-acid-free diets in lowering blood-pressure.

A most interesting parallel has been demonstrated between the known solubilities of colloid uric acid in the laboratory and the action of acids, alkalies and cold on the blood pressure.

Everything that clears the blood and urine of uric acid lowers blood pressure; everything which increases excretion in the urine raises it, but the effect is proportional, not so much to the dose of the drug as to the amount of uric acid it has to act upon.

No other explanation of the action of metals, acids, lithia, &c., on the blood pressure has been given except their effects on the solubility and excretion of uric acid.

The effect of uric acid or its salts (or practically any xanthin compound), is first to lower blood pressure, and then, as uric acid is passing in excess in the urine, to raise it.

The reactions in the blood of the substance which raises blood pressure, are those of uric acid, for every metal known to form an insoluble compound with uric acid clears it out of the blood, and consequently out of the urine; the mineral acids do the same.

It has been suggested that the substance in the blood is para-xanthin, but para-xanthin forms a soluble compound with hydrochloric acid (see Chemical Basis of the Animal Body, p. 178), while hydrochloric acid clears the blood of the substance we are looking for and lowers blood pressure, acting like other things which form insoluble compounds with uric acid.

The solubilities of uric acid completely explain the production of bradycardia by disease and the action of drugs in relieving or preventing it.

The causation of many forms of syncope is also explained, and many of those who suffer cease to do so under otherwise similar conditions, when their blood and urine are kept clear from excess of uric acid by means of diet.

A case in point is that of a Rugby boy, who suffered from migraine and temporary albuminuria, and fainted on several occasions. He was put on uric-acid-free diet, and has lived on it ever since. Now (fourteen years later) he is without migraine or albuminuria, and is capable of great and prolonged exertion (200 miles on a loaded cycle in twenty-four hours) without undue fatigue or any sign of syncope, with normal blood colour and blood pressure. Can there be any doubt that if diet had not been altered, this man would to-day be a chronic invalid with migraine and albuminuria or Bright's disease, and be quite incapable of athletic feats of strength and endurance? This reminds me that not a few who are now regarded as athletes were cripples on the old mixed diet.

The cause of many alterations in the rate of the heart's action becomes clear; as also the influence of drugs upon it, and the relation of hæmorrhage to high blood pressure, with the cure of the former by drugs.

Without this the supposed irresponsible action of the nervous system causes great confusion, and would force us to believe in the internecine warfare of nerve centres and physiological suicide.

No other explanation has yet been given of the relation between the excretions of uric acid and of water in the urine.

No other satisfactory explanation has yet been given of the limitation of Raynaud's disease to surfaces and extremities.

Nor is it easy to believe that any muscular tissue can possibly remain contracted a sufficient length of time to cause its own death from gangrene.

Whereas if the capillaries are mechanically obstructed by a storm of uric acid granules these may not only remain indefinitely undissolved, but are certain to do so the more the circulation slackens and the temperature of the part falls, for cold precipitates uric acid.

Anything that clears uric acid out of the urine and at the same time lowers blood pressure, may produce or precipitate an attack of gout in some fibrous tissue or joint, this showing where the uric acid has been deposited on leaving the blood, and why it fails to appear in the urine.

Where the heart does not complete more than sixty cycles in a minute, the radial artery rolled under the points of three fingers feels full between the beats, the arteriometer shows an unusually large diameter, and the pulse gives a tracing as in fig. 44; where the first sound of the heart is long, and the second sound both at the apex and over the aortic area loud, where the skin and extremities tend to get easily cold, and the urine and other secretions tend to be scanty, where the temperature in the mouth and rectum are far apart and are perhaps also, both of them, lower than in the corresponding hours of a normal day, there can be very little doubt about the presence of high blood pressure; and when it is present, and there is reason to believe it is doing harm, the obvious indication is to reduce it.

Now every drug mentioned in chapters ii. and iii. as diminishing the excretion of uric acid in the urine will, in doing so, lower the blood pressure, quicken the pulse and free the circulation. Which of these drugs will do this best under the circumstances present in a given case?

Speaking generally, those things will act most certainly which, like the metals and their salts, form directly insoluble compounds with uric acid, and are independent of the rise and fall of the alkalinity of the blood.

Acids and substances which act by raising the acidity of the

urine and lowering the alkalinity of the blood may obviously be overcome, or have their power reduced, by fatigue, heat, and perspiration, vomiting, diarrhœa and gastro-intestinal disturbances in general, which tend to lower the acidity of the urine and raise the alkalinity of the blood.

So that where any of these conditions are likely to be present, I make use of one of the metals, generally mercury.

And the action even of mercury is to some extent dependent on its not purging and not causing gastro-intestinal irritation or diarrhœa; if it causes mercurialism with salivation and gastro-intestinal derangement, its power over uric acid will quickly be reduced, and it will cease to lower the blood pressure or quicken the pulse.

Generally speaking, I rely with the utmost confidence on the action of mercury, or that combination of it with iodine found in the ordinary mixture, containing liq. hydrarg. perchlor. ʒi., and iodide of potassium gr. v., in which we get the retentive action of the iodide added to that of the mercury (see figs. 17 and 22).

The wonderful effects of mercury on the circulation are *noted* in an instructive case published in the *Lancet* (1895, vol. ii., p. 779), by Dr. Murray. Here cardiac tonics and stimulants were given up as useless, but mercury in the form of blue pill, taken to the extent of 20,000 grs., kept the patient alive for ten years, and during the whole time it neither purged nor salivated him, and if it had done either of these it would not have acted on the circulation nearly so well as it did.

Dr. W. Russell says, in an article on "Arterial Sclerosis" (*British Medical Journal*, vol. i., 1904, p. 1298), "The effect of mercury on the condition is universally recognised; it promptly lowers the arterial tension, not by acting on the heart and diminishing its vigour, but by relaxing hypertonus."

It is certain that mercury as it lowers this tension, clears the blood of uric acid, and every other drug or metal which clears the blood of uric acid does the same. Diet which keeps uric acid out of the body produces this effect, but more slowly.

With regard to mercury there is another substance with similar effect, though as a rule it is not so powerful. This is a salt of calcium such as the chloride. In the *British Medical Journal*, vol. i., 1906, p. 797, an article by Dr. C. Arbour Stephens on the "Use of Calcium Salts in Chilblains" attracted my attention, because chilblains are things to which meat-eaters are specially liable, losing their liability on giving up meat and tea, and thus escaping collæmic conditions. Probably in these conditions a salt

of calcium acts (like many of the other drugs discussed) on the solubility of uric acid, and thus on the capillary circulation of the skin.

In the *British Medical Journal*, 1906, vol. ii., p. 138, the same author writes on the "Value of Calcium Iodide in the Treatment of Ulcers." Seemingly this salt has a remarkable effect in promoting the healing of various forms of chronic ulceration. This salt presents a double retentive action as regards uric acid, for urate of calcium is insoluble, and iodine in the form of iodide also interferes with solubility.

I believe the iodide of mercury to be the most powerful of the retentive drugs, but possibly the iodide of calcium has similar powers. The author speaks generally of the effects of calcium on health and disease, but probably its healing influence is due to its action on the solubility of uric acid, thus coinciding with the action of opium and mercury. Yet the iodide of calcium may be more useful than mercury, since this has its dangers—a patient who suffers from mercurialism passing into a more or less serious condition. A retentive drug with action nearly as powerful as that of iodide of mercury, with freedom from its dangers, would be valuable indeed in collæmic trouble.

In the *Lancet*, 1906, vol. i., p. 143, occurs a paper by Dr. G. W. Ross on the "Relief of Certain Headaches by the Administration of Salts of Calcium," the salt he used being apparently the lactate. He mentions that it acted well in two cases of undoubted migraine. These headaches were of the lymphatic type, and were associated with deficient coagulability of the blood and œdema of the tissues; in fact, they were allied to conditions described as "serous hæmorrhage," and he found accompanying pain after food, œdema of face or extremities, chilblains, or urticaria and neuralgia. I have pointed out the relation of these troubles to uric acid collæmia, and evidently this lymphatic headache is the ordinary uric acid migraine, the œdema of the tissues being a result of the raised blood pressure and capillary circulation obstructed by uric acid, of which we shall see some interesting instances later, especially when dealing with the circulation within the skull. This lymphatic headache is a stepping-stone between the usual phenomena of migraine and the "serous hæmorrhage" common in uræmia, where the brain is often found *post mortem* to drip water like a sponge.

With regard to the lowered coagulability of the blood, I consider it a result of hydræmia, for the effect of excess of uric acid in the blood is to increase its coagulability (see cases mentioned in chap.

xi.). With much retention of water in the blood and tissues, this hydræmia may diminish the coagulability, and possibly it is by clearing out the uric acid and allowing the water to run off that the calcium salts diminish hydræmia and increase coagulability.

Dr. Ross has thus treated cases of Bright's disease, and his experience shows us that the salts of calcium would act in this disease in much the same way as the iodide of mercury. Clinically it is easy to distinguish between a headache due to high blood pressure and one due to œdema.

Most cases of migraine can at once be relieved by the application of a tourniquet in the neck or any mechanical means of lowering the blood pressure within the skull. But in the cases of real œdema of brain membranes (in uræmia) this would not be sufficient; it would be necessary to drain off the fluid as well as to lower the pressure.

Some believe the cure of albuminuria by calcium salts to denote that it is not of the nature of Bright's disease. This is far from the truth, for all these albuminurias, including those of undoubted Bright's disease, are consequences of defective metabolism, which again is the result of defective capillary circulation, the sequence of excess of uric acid in the blood.

But this so-called cure, whether by calcium salts (lactate or iodide), or any other substance which forms an insoluble compound with uric acid, is but temporary relief from the clearing of the blood of uric acid by retention, and the permanent cure is the exclusion of any unnecessary uric acid from the food, resulting in the gradual disappearance of excess of this substance.

If mercury fails owing to gastro-intestinal disturbance, the only thing to do is to treat the gastro-intestinal condition with bismuth, opium and similar drugs, for probably nothing will affect the uric acid till this has been done, though a subcutaneous injection of morphine may be tried.

When we have to treat slight conditions of high blood pressure, and physiology in general is but little disturbed, a simple acid mixture will suffice, as nitro-hydrochloric acid with perhaps the addition of a little strychnine.

If we want to act very quickly the nitrites are best, or a small injection of morphine, and their action may be continued by the use of ammonium, or the iodides of sodium or potassium, or of wine, ether, and similar stimulants.

If we want to act steadily over a long period of time the iodides are most useful, or the iodide of mercury if it does not upset physiology; in this case try other metals, as zinc or copper.

All these drugs clear the blood of uric acid, lower the blood pressure, and free the interstitial circulation as a result; but they clear it *from* the blood into the tissues, and do not eliminate it from the body, and this must be remembered, for when they are stopped the uric acid thus held back will tend to get into the blood again, and the last state of the patient may be worse than the first.

A course of salicylates for five to ten days will overcome this difficulty, either with the last doses of the retentive drug, or immediately after it; this will carry off the stores of uric acid and prevent their doing any harm.

I may mention also that when mercury is contra-indicated, we have a valuable means of lowering the blood pressure in a course of acids and salicylates given concurrently—the acid mixture before meals and the salicylate after.

The acid prevents the uric acid from combining with neutral phosphates or alkalies in the blood (these being the compounds which appear especially to affect the blood pressure, and the compound of salicylic acid with glycocoll hardly, I think, affects it at all), while the salicylate holds it in solution and passes it out of the body, so that this treatment has the advantage of being followed by no rebound; or salicylate with an iodide may be used for the same purpose.

Diet, of course, by reducing both the introduction and formation of uric acid, offers the most permanent and satisfactory means of lowering blood pressure, and of this I shall speak in chapter xvii.

We must not forget that there is another factor in high blood pressure besides the uric acid, namely, the amount of fluid available.

With the same amount of capillary obstruction by uric acid the pressure will be higher in that vascular system in which there is the largest amount of fluid, and fluid and capillary obstruction being equal it will be highest in that system which has the strongest heart.

We have then three factors to deal with—(1) capillary obstruction, which varies with and is dependent on the amount of uric acid; (2) the quantity of fluids in the vascular system; and (3) heart power.

With regard to (2), I note that Dr. L. Hill says in the *Journal of Physiology*, vol. xxviii., p. 136, "Intravascular injections do not raise the arterial pressure (when the circulation is proceeding) by materially increasing the mean hydrostatic pressure of the system, but by increasing the diastolic filling and so the systolic output of the heart." We shall see in chapter vi. the great effect of this increased or diminished systolic output in increasing or diminishing the high-blood-pressure pain of migraine.

In physiology (1) and (2) vary obviously from hour to hour, and in pathology they are largely under our control; while (3) can be influenced by tonics on the one hand and depressants on the other.

Consider a case of hæmorrhage: we must enquire first of all whether it comes from the arteries or the capillaries and veins, whether from the distal or proximal side of our screw clamp in the imitation circulation previously mentioned. If from the capillaries on the distal side of the clamp the obvious indication is to screw up the clamp, and this is, I think, the way in which ergot stops such hæmorrhage as that from the uterus, though even here high blood pressure has some influence in increasing the flow. But when the hæmorrhage is arterial, as from an eroded vessel in the stomach or the lungs, or a ruptured vessel in the brain, the indication is to lower blood pressure by relaxing the screw clamp as much as possible; and this is, I believe, the way in which such drugs as opium and lead relieve, their first action being to clear the blood of uric acid and lower blood pressure; and we must beware that their second action or rebound (see fig. 35) does not occur too soon, *i.e.*, before the vessel is securely plugged, or the hæmorrhage will return.

If arteries the size of the radial dilate with every rise of blood pressure as the arteriometer shows, the great importance of reducing blood pressure in arterial hæmorrhage is obvious, and these considerations led me to use the iodide of mercury mixture in the treatment of hæmoptysis, with results which have often seemed to be very satisfactory. It acts in the same way as lead, opium, and other things more commonly used.

My friend, Mr. J. E. Frazer (formerly House Physician at the Metropolitan Hospital, and afterwards one of the Residents at the Royal National Hospital, Ventnor), tells me he has often seen it used with benefit, especially in hæmoptysis, coming in the morning hours and associated with headache (? hæmoptysis due to collæmia). I found, however, that the hæmoptysis returned after the mercury and iodide, till I took to following it by salicylates. Prof. Mays (*New York Med. Journ.*, 1896, 27th June), has been led by my statements to use salicylates with success in a case of phthisis, with pains in the chest and arms, and also in some kinds of hæmoptysis (see also *Philadelphia Polyclinic*, vol. v., Oct., 1896).

It may be of interest to remember that Mr. J. Hutchinson has pointed out in his "Archives of Surgery," that a very reliable method of curing epistaxis is to plunge the hands and feet in very hot water, for such treatment would put a stop to local collæmia, and by returning warm in place of cold blood to the deeper parts would no doubt

soon revive the temperature of the whole mass of the blood, clear up collæmia in general and lower blood pressure. Similar treatment is valuable in the uric acid headache, no doubt also from the effects on collæmia and blood pressure.

I have several times seen epistaxis come on during exposure to cold, and it seems very probable that the common running of water from the nose is a minor condition of the same thing, and represents the physiological result of the collæmic obstruction of vessels and high blood pressure which cold produces. Carry this a step further and the congestion of the vascular mucous membranes of the nose is so great as to cause hæmorrhage; apart from any marked action of cold, such hæmorrhage is in my experience most common in the a.m. hours, when there is for other reasons most collæmia.

I have also seen much epistaxis in which there appeared to be a recurrence in the spring corresponding with the collæmic high blood pressure so common at this season, and its relation to sexual activity and the incidence of mental disease.

Such was the position reached by means of the old instruments, the sphygmograph and the arteriometer; we knew that a rise in the excretion of uric acid in the urine was accompanied by a sphygmogram showing a large first wave high up in the tracing, by an increase in the diameter of the radial artery, by a scanty hourly excretion of water in the urine, by an increasing distance of separation between surface and deep temperatures, and by a diminishing excretion of urea.

We knew that by controlling uric acid we could practically cause any alterations in its effects on the circulation and its above-mentioned results.

A considerable amount of time was required to make all these observations. A satisfactory sphygmogram could not be obtained under several minutes; to measure the diameter of the artery took several more; to collect and separate the urine from hour to hour, and to take the temperatures in the mouth and rectum caused much delay, so that a complete observation, to say nothing of the daily collection and estimation of the urine, could not be made in much less than thirty minutes.

The quantity of uric acid in the blood can now be estimated from the granules in from thirty to forty minutes, and though this did not save much time, it later on with other tests afforded me the means of estimating with sufficient accuracy for most practical purposes the amount of uric acid in the blood in possibly a few seconds, certainly something considerably under five minutes.

This enables us to get much closer to our work, to obtain a better grasp of it, and to follow uric acid and all its fluctuations throughout the twenty-four hours with greater completeness and more valuable results.

I had long realised that if I could measure the rate of the capillary circulation with accuracy I should get the test I wanted.

And after attempting for several years to measure the rate of capillary circulation in the eye, I eventually adopted the following process for taking the rate of disappearance of the fatigue image or "after-image," produced by exposing the eye to a constant light at a constant distance and time.

The time of exposure and of the duration of the "after-image" were measured by the metronome, and I adopted the following procedure :—

An ordinary bull's-eye gas lamp, as used for the laryngoscope, is placed at a known distance from the head in a dark room. The light is turned on but the shutter is kept over the bull's-eye (I found that the pressure of gas is sufficiently constant from day to day to regulate the light for comparative purposes). The metronome is then set working, and at a given beat the shutter is pulled down and the full light falls on the eyes ; after ten half seconds at a given beat of the metronome the gas is turned out, and the room is in darkness, time being measured by the stroke of the metronome.

The eyes are kept open, and what they see is a bright image of the bull's-eye growing less bright until the centre of the bull's-eye is almost black, while its outer edge remains relatively bright.

It became necessary to fix upon some definite point in the phenomenon of the fading image, and I took the most definite one, namely, the point at which the outer ring of the circle became distinctly brighter than the centre.

But long before this it had become evident that the after-image faded more quickly in the evening, and less quickly in the morning, and that, in fact, it followed every fluctuation in the amount of uric acid in the blood and urine, being slower in the morning with more, and quicker in the evening with less, uric acid.

I am indebted to Dr. Bruce, of Grimsby, for the suggestion that collæmia accounts for diminished acuteness of vision under certain conditions ; thus he has noticed that riflemen from the north do very badly at Bisley when the weather is hot. The hot weather would produce in the less accustomed north-countrymen considerable collæmia, and thus cause defective circulation, slow recovery from fatigue and diminished acuteness of vision. We must bear in mind

that defective circulation influences not only the retina but the brain, the cord, the nerves and the muscles, and that the result, defective shooting, is probably due to its effects on all. Dr. Bruce mentions a Queen's prizeman who made his highest scores when suffering from muscular rheumatism, and thus in a condition in which his blood would be fairly free from collæmia, and the capillary circulation good in consequence. Here defect due to local muscular pain was counterbalanced by the advantage of free circulation in the nerve centres and the retina.

An observation made by Raynaud, led me to the more generally useful measurement of the rate of capillary circulation in the skin. He remarks that when the vessels in the skin of a finger affected by local asphyxia are emptied by pressure, as much as thirty seconds may elapse before it regains its colour, while in the skin of a normal extremity the colour returns in one or two seconds. I reflected that if there is this difference between the normal and the pathological returns, and if Raynaud's disease is, as I have suggested, due to collæmia, I might find differences corresponding to the fluctuations of uric acid produced in physiology, pathology and by drug action, differences not so marked as those above mentioned, but still clinically useful. I accordingly began to measure experimentally the times of what I now call the capillary reflux—that is, the time in which the colour returns in, say, a given area in the back of the hand, when removed by pressure. After a time I adopted an instrument* which gives a constant definite area of pressure, the pressure being applied for a constant time, measured by a metronome beating half seconds, the length of time the blood and colour take to return being similarly measured. That I might watch and control the results of these processes I kept them in action over many months of daily estimation of the urine, all results being recorded in curves (some of which I give in the following figures), and I observed at the same hours either the size of the radial artery by Oliver's arteriometer, or the blood pressure by the Hill Barnard sphygmometer,† and the pulse rate, and added occasional observations of temperatures and blood granules to test the other results.

The whole of these tests recorded in the most striking manner all the marked fluctuations in the excretion of uric acid, whether due to physiology, drug action or pathology. Thus in physiology the capillary reflux takes in the morning (7 a.m. general time of obser-

* To be obtained from Hawksley, 357, Oxford Street, and which he calls a capillary dynamometer, price 10s. 6d.

† Made by Hicks, 10, Hatton Garden.

vations) 5 to 6 half-seconds; in the evening (10.30 to 11 p.m.) 4 to 5 half-seconds or less. The after-image reaches a certain stage in disappearance in the morning in 80 to 90 half-seconds, and in the evening in 70 to 80 half-seconds. The pulse rate is slower in the morning (68), and quicker in the evening (72 to 76); the arteriometer gives measurements in the morning of 1·2 to 1·3 mm., and in the evening 1·0 to 1·1 mm., and the sphygmometer records blood pressures of 120 or 130 in the morning, and 95 to 105 in the evening.

In pathology, at one extreme are capillary refluxes of 7 in a slight headache with a blood pressure of 140, and at the other extreme, refluxes of 8 to 10—12 or more in Bright's disease with blood pressures of 160 to 180, and arteriometer measurements of 1·8 to 2·0 mm. or above. Or, on the other hand, in fever a reflux of 2 to 3 or under 4 half-seconds is common, and a blood pressure of 70 to 100. And a patient who has a reflux of 3 or 4 during a fever, such as enteric, will have a reflux of 7 or 8 in the subnormal temperature period which follows the fever.

In drug action it is possible to make almost any variations on the normal readings of physiology; thus the normal curves can be inverted, making the highest blood pressures and slowest capillary refluxes in the evening instead of the morning, or the fluctuations diminished, making the curves almost into straight lines with little variation between morning and evening; great general changes of level can be produced by the action of salicylates on excretion, or a single dose of this drug taken two or three hours before the evening observation will convert the normal fall of pressure into a rise, and cause a slow capillary reflux in place of a quick one. With this same drug we can cause identical fluctuations in the number of blood granules.

It is impossible to control the blood pressure and capillary circulation curves except by controlling the excretion of uric acid in the urine and the number of granules in the blood; as these latter can be controlled so now can the capillary reflux and the blood pressure. In the observation of the capillary circulation we have a test applicable to anyone, at any place and time, and practically without instruments; for differences such as those between the 2 or 3 half-seconds of fever, and the 7 or 8 half-seconds of collæmic headache or depression, and still more the 8 to 10 or 12 half-seconds of Bright's disease, are sufficiently marked to be seen with no more accurate instruments than the point of the finger and the second hand of the watch, or even without the latter by merely counting time.

With regard to the capillary refluxes on the back of the hand there are two important points: (1) See that the hand is at or about the same level as the heart at the time of the observation; (2) do

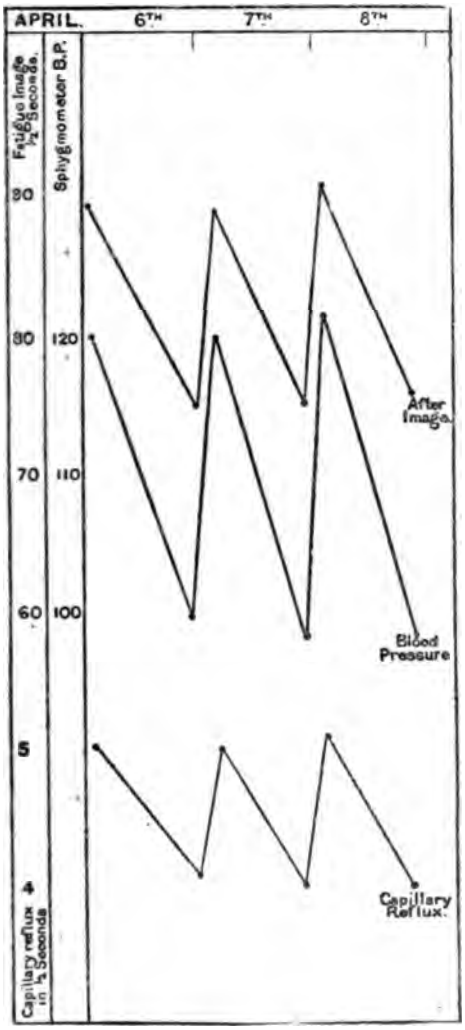

FIG. 38.—NORMAL CURVES OF AFTER-IMAGE, BLOOD PRESSURE AND CAPILLARY REFLUX, MORNING AND EVENING.

not trust observations on a hand which differs a good deal from the temperature of the rest of the body. With a patient in bed a hand brought from beneath the bed clothes will probably give correct

results; but if it is outside and feels cold without the veins showing, the capillary reflux will be too slow. This, however, does not greatly affect fever, as the capillary reflux will be notably fast in a febrile patient, even though the extremity is cool or cold. Where the hand

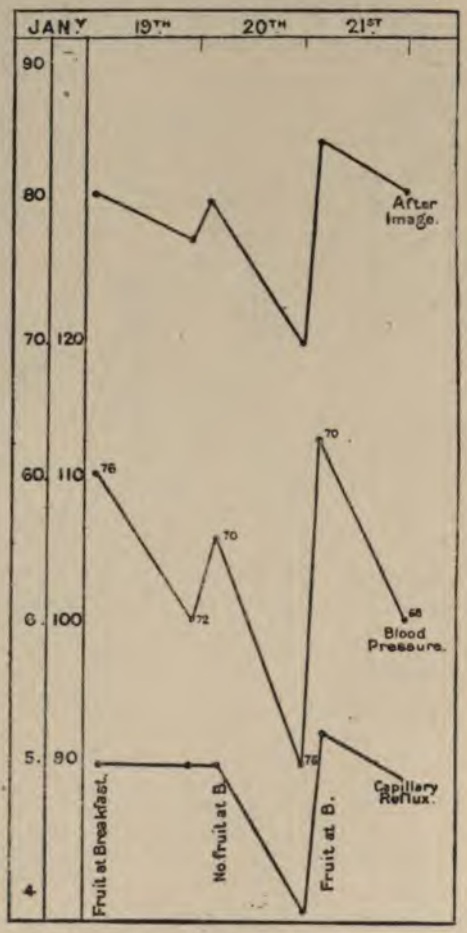

FIG. 39.—CURVES OF AFTER-IMAGE, BLOOD PRESSURE AND CAPILLARY REFLUX, SHOWING EFFECTS OF DIET.

is too cold, make the observation on the front of the chest at the heart level, or on any part if the patient is horizontal in bed; but it must not be made in dependent parts below the heart level, or where the venous circulation is obstructed *e.g.*, by pressure of clothing, or

in thrombosed, inflamed or congested limbs, all of which will show local quickening of the reflux.

The "after-image" test is not so generally useful, depending much on the training and powers of observation of the patient; I have used it chiefly in myself that I might allow for the disturbing effects of cold weather on the capillary reflux of the skin. It gives very marked results in all the larger fluctuations of the other circulation curves; and these results can probably be repeated by anyone after a few days' practice.

Children, as a rule, are slower than adults, and there are slight individual variations, but never of sufficient importance to obscure the main results in pathology, though here and there they may render physiological results less clear than in the given curves.

Fig. 38 shows the normal diurnal fluctuation of physiology, the capillary reflux slow in the morning and quick in the evening, the blood pressure high in the morning from millions of obstructed capillaries, and low in the evening because they are freer, and the "after-image" slower of disappearance in the morning and quicker in the evening, probably because the effects of fatigue are more quickly made good, the better the capillary circulation. The fluctuations of all three are due to, and correspond with, the well-known diurnal fluctuation in the excretion of uric acid and the amount passing through the blood into the urine. Fig. 39 shows the effects of diet on the excretion of uric acid and so on the form of the curves. Acid fruits were taken at breakfast on the mornings of the 19th and 21st, but were replaced by potatoes containing alkali on the morning of the 20th. The effect of taking acid fruits at breakfast is to diminish the morning excretion of uric acid during the following hours, and the uric acid retained in the morning tends to enter the blood in the afternoon and evening, and prevent the usual evening fall of blood pressure due to quickened and freed capillary circulation. Hence, on the 19th and 21st there is little of the normal diurnal fluctuation; on the 20th, with a normal excretion of uric acid in the morning, the fluctuation is normal. The acid fruit was taken at breakfast, after the morning observation had been made, so it did not directly affect this result; it did, however, affect the evening, and thus the extent of the daily fluctuation.

A similar flattening out of the curves is produced by any other method of equalising the excretion of uric acid throughout the twenty-four hours; thus, a dose of alkali at night will, after a night or two, diminish the excretion of uric acid in the a.m. hours, and prevent part of the morning slowing of capillary circulation and rise

of blood pressure. In the same way a course of alkali or a course of salicylate will, after a few days, diminish the amount of available uric acid, and more or less equalise its excretion throughout the twenty-four hours, the curves following and demonstrating these results. The first effect of a course of salicylate is a larger excretion of uric acid in the evenings than in the mornings, and the capillary circulation is slower and the blood pressure higher in the evening than in the morning, the normal curves of fig. 38 being thus absolutely reversed; while a single dose of salicylate taken after dinner will prevent more or less the usual evening freeing of capillaries and fall of blood pressure. The effect of salicylate in slowing the capillary reflux is seen in an exaggerated degree in acute rheumatism, where a capillary reflux of four during the fever, alters to eight, ten, or above, as the temperature falls under salicylates, thus demonstrating a large excess of uric acid in the blood as the joint pains are relieved. A single dose will produce a similar though less marked effect in physiology, and in both cases a proportional increase of blood granules marks the change from the quick to the slow reflux. Fig. 40 shows the somewhat similar effects of weather, for exposure to cold during the morning and afternoon of the 19th diminished the a.m. and early p.m. excretion of uric acid, and adding it on to the evening produced a slight rise or, at least, an absence of fall. The other two days are more or less normal, though the 20th is slightly affected by the altered excretion of the 19th. The practical conclusion is, never expose yourself to cold, especially in the morning hours, for cold means retention of uric acid, and for every hour of retention you will have an hour of collæmia on some future day. Absolute freedom from uric acid requires that you shall not swallow, and also that you shall not retain or accumulate it. It will be noted that the curves in parts of this figure do not strictly correspond; unavoidable errors prevent it, but these errors have not been sufficient to obscure the main fluctuations, which are practically the same for all.

If we control uric acid—and this can be shown by examining the urine and blood hourly—we control the curves, but if we fail to control it, we also fail to alter the curves; such experiences have given me the most complete confidence in the accuracy of the results, as I have sometimes found the curves rising when I expected a fall, or falling when I expected a rise; and on subsequent examination of the blood and urine I have seen that some other force had moved the uric acid in the direction I least expected. Fig. 41 shows the straightening of the curves during the low excre-

tion of uric acid which succeeds a course of salicylates; a very similar effect can be produced by a course of alkali. On the 8th it

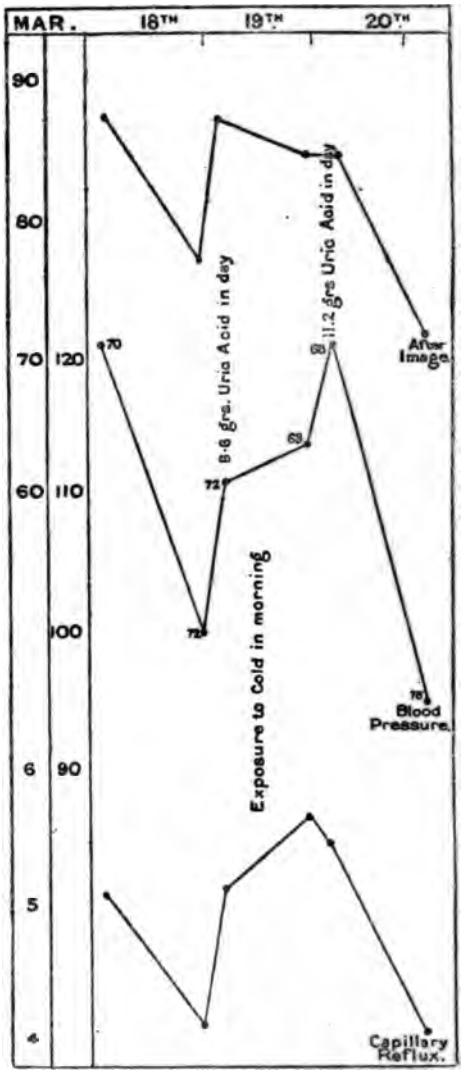

FIG. 40.--CURVES OF AFTER-IMAGE, BLOOD PRESSURE AND CAPILLARY REFLUX, SHOWING EFFECTS OF WEATHER.

also shows a fluctuation in excretion, with slow capillary circulation and high blood pressure in the evening, producing slight headache

and a pulse of 66, during which the blood granules rose to the relation of one to four red cells: such a fluctuation and headache being a common result of the oscillations in excretion which follow

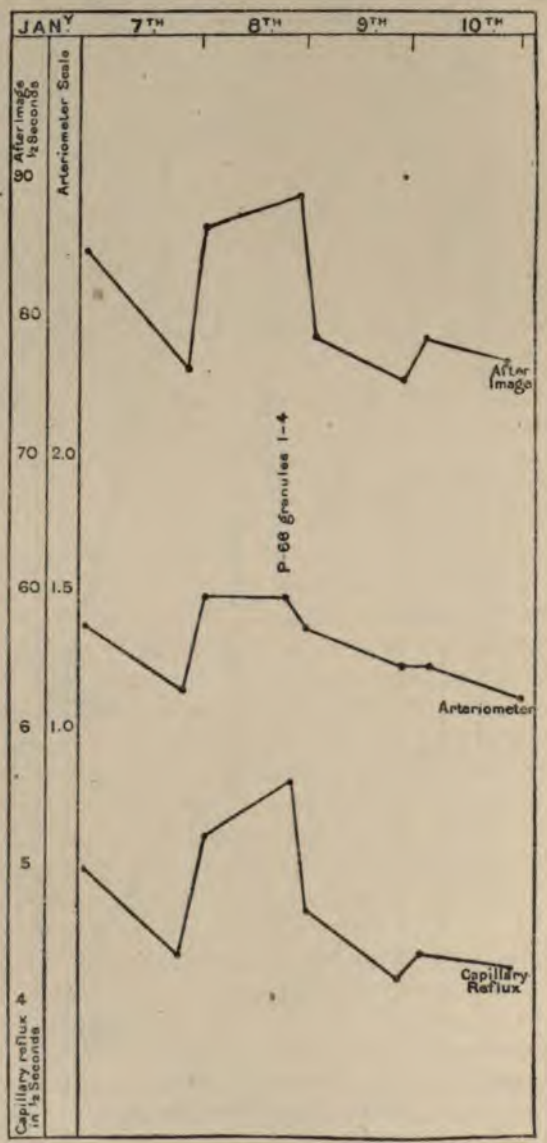

FIG. 41.—CURVES OF AFTER-IMAGE, ARTERIOMETER AND CAPILLARY REFLUX, SHOWING THE FLATTENING OUT THAT FOLLOWS ON TAKING SALICYLATES, AND THE FLUCTUATION OF A HEADACHE.

the use of these powerful excretants. In this figure the middle curve is that of the diameter of the radial artery, as obtained by Dr. Oliver's arteriometer in place of the sphygmometer curves in the other figures; though the sphygmometer shows the fluctuations better, and the errors with it are relatively less, as pointed out by its inventors. The thermometer also will corroborate these results in the case of slowing of the capillary reflux and the high rise of blood pressure accompanying a headache; for this gives the test which Marey originally pointed out as the sign of contracted surface vessels (it is really the sign, I think, of obstructed capillaries, and of capillaries obstructed by uric acid, for uric acid will obstruct the vessels of the exposed surface and extremities, and to a less extent those of the deeper tissues). This sign consists of a wide separation between the temperature in the mouth and that in the rectum, and in headache and all collæmic conditions we find a larger distance than usual separating the mouth temperature from the rectal. On an evening of headache with curves similar to the above, the mouth temperature was 97·6°, the rectal 98·6°, a whole degree apart; while on the following evening, with normal curves at the same hour, it was in the mouth 98·0°, and in the rectum 98·4°, less than half a degree apart.

I have asserted that I could produce a headache at will by causing similar fluctuations in the excretion of uric acid; but by watching these morning and evening fluctuations one sees the real cause and effect, and obtains a power of control correspondingly greater. Fig. 42 shows the effect of a rise of temperature. Here on the 23rd and 24th the curves of capillary reflux and after-image are fairly normal: but on the morning of the 25th the mouth temperature was 99·6°, and this sufficed to keep the capillary reflux as quick, or slightly quicker, than on the previous evening. Here again the thermometer would corroborate results, as the temperatures in the mouth and rectum are close together, with rising fever; and another common coincident result testifying to free capillaries in the kidney is a diuresis.

I have observed these physiological fluctuations (fig. 38) in many people; and as all practically are alike, I have not kept records; anyone can duplicate these results or some of the modifications shown in other figures. Pathological conditions of high blood pressure, such as Bright's disease, tend to show higher blood pressure, slower pulse rate and slower capillary reflux in the morning, and lower blood pressure, quicker pulse rate and quicker capillary reflux in the evening; and these have doubtless the same causation as

those of physiology, and can also be controlled materially by diet, weather, clothing, and drugs which influence the quantity and solubility of uric acid in the blood.

These tests are practically measurements of the amount of uric acid in the blood, and are accurate enough to correspond to the well-known diurnal fluctuations in its excretion and the modifications

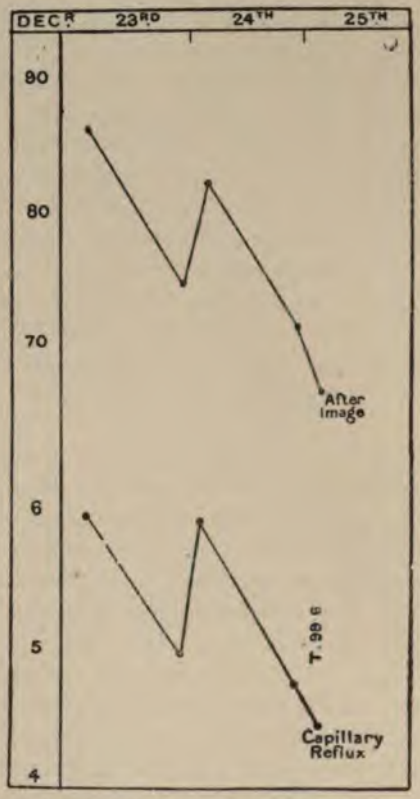

FIG. 42.—CURVES OF AFTER-IMAGE AND CAPILLARY REFLUX SHOWING EFFECTS OF RISE OF TEMPERATURE.

induced by weather, and by drugs. Still more clearly do they show the pathological alterations produced by Bright's disease contrasted with fever. The results of these tests can be corroborated by the direct examination of the granules in the blood itself; by testing the hourly excretion of uric acid in the urine which (fig. 21) corresponds hourly with the number of granules in the blood; by measuring the hourly excretion of water in the urine, the water

expired from the lungs, or the distance between mouth and rectal temperatures.

Thus fig. 43 shows the excretion of uric acid, the blood pressure and capillary reflux curves night and morning for eight days.

Uric acid is high and blood pressure and capillary reflux are also somewhat high in the morning.

On the 18th a retentive drug is given, uric acid falls decidedly, and there is a very low blood pressure and a quick capillary reflux at night.

On the following days the evening falls of blood pressure are less and less marked, while the morning points fall somewhat.

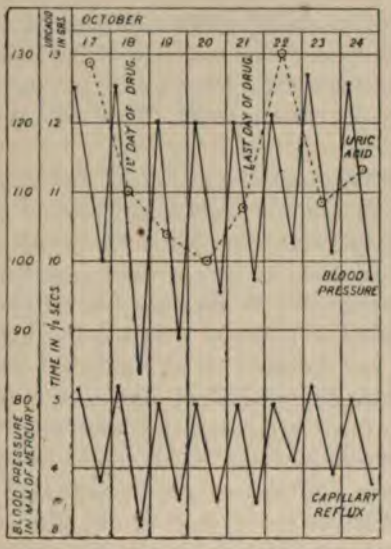

FIG. 43.—CURVES OF BLOOD PRESSURE AND CAPILLARY REFLUX IN RELATION TO THE CURVE OF URIC ACID EXCRETION OVER A SERIES OF DAYS.

The 21st is the last day of the drug, and on the 22nd uric acid has resumed its original height. The morning points rise a little, especially on the 23rd, the morning of the 22nd being still somewhat under the influence of the drug; and the evening of the 22nd shows a relatively diminished fall pointing to an increased excretion of uric acid that day and evening, and on the morning of 23rd; that being the first "alkaline tide" in which the excretion of uric acid is free from the drug.

A similar though more marked diminution of the evening fall with a plus excretion of uric acid is seen in fig. 40.

The significance of the figure as a whole is that the retentive drug affected especially the evening hours, because though taken in the morning it was too late to affect more than a portion of the alkaline tide, hence the low falls in the evenings at the beginning of the figure. Later these were less marked because the uric acid accumulated and tended to overflow, and when the drug was stopped the evening fall very greatly diminished.

I was estimating the blood granules every morning about 10 a.m. at this time, and I omit their curve as making the plate too complex. It is nearly identical with the uric acid as the granules were at their lowest, 1 to 18 on the 20th, and at their highest, 1 to 8 on the 22nd and 23rd.

Here the granules corroborate the circulation curves of the 23rd and reveal a large quantity of uric acid in the blood on the morning of the 23rd; this diminished later on in the day, and especially in the evening, so that the excretion for the whole twenty-four hours fell considerably.

The best test, because of its simplicity and speed, is the capillary reflux. For clinical work it practically requires no instrument, the habit of counting half seconds with sufficient accuracy being easily acquired. It is possible to take a ward spending less than half a minute at each bed, and to separate out the cases of fever, and those of post-febrile sub-normal temperature, high blood pressure, Bright's disease, and diabetes, all of which are conditions of defective (because obstructed) capillary circulation, the defective combustion and high blood pressure being the result. If there were a case of Raynaud's disease the result might be more marked than in any of the above. When using it for pathology we must recollect that children are rather slower than adults, just as they have generally more granules in the blood and more uric acid in the urine. Also that the quick reflux of fever may be slowed somewhat by conditions of dyspnœa and cyanosis, these tending to increase uric acid in the blood and urine, thus antagonising the effects of fever, and relatively slowing the capillary reflux.

I will give a few notes to illustrate this point. Emily C., aged 19, suffering from advanced mitral constriction and infarcts in the lungs. Considerable dyspnœa, expectoration slightly blood-stained.

Temperature: great diurnal variation, 99° in morning to 102° and 102·8° in the evening. Pulse 100; respiration 40; capillary reflux 7 to 8; blood pressure 120 to 130.

The dypsnœa caused a rise in the alkalinity of the blood and flooded it with uric acid in spite of the rising temperature, hence the morning collæmia was great and kept the temperature down.

In the evening with less collæmia and higher acidity it rose decidedly.

As a result we had slow capillary reflux and high blood pressure in spite of fever, and if the temperature in mouth and rectum had been compared they would have been found several degrees apart, especially with the lower morning temperature, showing that the mouth temperature was lowered by obstruction of capillary vessels of which the slow capillary reflux and high blood pressure were other signs.

There was no low blood pressure because the fever failed to render the blood a bad solvent of uric acid. It failed badly in the morning and only slightly in the evening, and we know why it did so, for in the morning, just as in physiological conditions, there was more alkali and more uric acid, and in the evening less.

Capillary reflux and blood pressure were an accurate guide to the amount of uric acid in the blood. Here we have one of the conditions of dyspnœa and deficient oxidation in which, as pointed out by Professor von Jacksch and others, there is excess of uric acid in the blood, but with the explanation unknown to them that such excess is a matter of uric acid solubility and not of new or extra formation.

Had this patient been for some two or three years on a uric-acid-free diet the above signs of excess of uric acid in the circulation would have been but little marked, perhaps invisible, in spite of the heart lesion and dyspnœa. And with a life-long diet the fatal heart lesion would not have occurred.

The practical point is that slow capillary reflux does not exclude some fever when there is dyspnœa.

On the other hand, the slow reflux of Bright's disease and similar conditions may be quickened by venous congestion, whether local, as produced by a ligature round the arm (as pointed out by Raynaud), or general, and due to cardiac or thoracic disease or obstruction.

We have then two causes of quickening of the capillary reflux: (1) Freedom of capillaries from obstruction by collæmia, and (2) obstruction in front between the capillaries and the heart on the venous side. I had an illustration of this in a patient (girl, aged 10) at the Metropolitan Hospital in the last stages of rheumatic morbis cordis. She had as a complication thrombosis of some of the veins on the left side of the neck causing, among other things, œdema and venous congestion of the left arm. The house-physician, Dr. Jenkins, noticed that her capillary reflux was slower in the right arm than in the left, and I then found that it was 9 in the right arm

(that is, slow because of dyspnœa, cyanosis and general failure of the circulation) and 6 in the left. Here blood pressure was low (only 70 to 80), but there were present all the conditions of capillary circulation that would have produced high blood pressure if the heart had been equal to the task. The slow reflux in the right arm was due to the collæmia of low nutrition, cyanosis and dyspnœa, and this was distinctly quickened in the left arm by venous congestion, due to the thrombosis. I use the test with confidence in the out-patient room, where it enables me to pick out cases of high blood pressure and Bright's disease, or to say when a temperature should be taken, or where a coated tongue, or a pulse perhaps quick from momentary excitement are not accompanied by fever.

The test is thus of wide clinical value apart from the fact that it is a guide to the blood pressure and its cause—the amount of uric acid in the blood. And when we realise that the defective circulation thus seen is a correct index of the condition of the body from the highest capillary to the lowest, we understand in part what an immense power is thus exerted by uric acid over the circulation, nutrition, and function of the whole body and all its tissues; also the way in which it controls the intravascular pressure and the work of the heart; and partly through the capillaries, partly through the blood pressure, dominates the function and nutrition of the great nerve centres. Uric acid is thus proved to be a cause not a consequence, and its headache the epitome of a wide field in pathology.

The association between high blood pressure and a large excretion of uric acid in the urine, first observed in this disease, is one instance of a general law. The headache is the mechanical result of high blood pressure, and this is the mechanical result of capillaries obstructed by colloid uric acid. The low and falling urea which accompanies the headache is the first intimation of the defective combustion (Bright's disease) in which the untreated headache ends.

Knowing the relation of blood pressure to uric acid, and of uric acid to age and time of life, we can sketch that of blood pressure and circulation in few words. Life may be for this purpose divided into four stages: (1) high nutrition and rapid metabolism of growth up to 13 in girls and 16 in boys, see fig. 59; (2) slackening of metabolism and nutrition at the end of growth, 17 to 25, most marked in girls; (3) maintenance of good nutrition, prime of life and after, 25 to 50 or 55; (4) decline of life to old age, 55 to 75 and after. Period number (1) is a time of retention, period (2) is a time of excessive excretion following it, period (3) is a time of renewed retention, and

period (4) is a time of final excessive excretion from the stores formed in (3). There are thus two retention periods (1) and (3), and two collæmic periods (2) and (4). The two great groups of diseases in the main correspond with these. In number (1) (childhood) we have low blood pressure, retention of uric acid, and high blood quality from active metabolism with high acidity, in association with such diseases as acute rheumatism, acute bronchitis and acute skin diseases—diseases of the retention group (see pages 134 and 135). In number (2) period we get collæmia from the passage into the blood of the uric acid retained in number (1) period, and the diseases of this second period are collæmic diseases, such as chlorosis, anæmia; headache, epilepsy, hysteria, asthma, depression and suicide, with high blood pressure. In number (3) stage the collæmic diseases pass off, and those of good nutrition and retention of uric acid succeed, such as gout and rheumatism in one form or the other, with diminishing anæmia. In number (4) appear the results of the retention of uric acid, in number (3) the return of uric acid into the blood-producing collæmia, high blood pressure, increasing anæmia, depression, suicide, pernicious anæmia, Bright's disease, glycosuria, diabetes, obesity and all defective combustion diseases of the final collæmic period. The collæmic diseases of the second stage are proportional to the introduction of food poisons and to the retention of uric acid in number (1) stage, and similarly the collæmic diseases of number (4) stage are proportional to the introduction and retention of uric acid in number (3) stage.

These rules are fixed, but there will be small individual variations. The high blood pressure and anæmia of old age are the parallel of the high blood pressure and chlorosis beginning at 17. In both cases the collæmic group of diseases is proportional to the retention of the preceding period, as well as to the fall of nutrition precipitating the collæmia. In old age the severity of collæmic diseases is proportional partly to the failure of nutrition and partly to the amount of uric acid stored in number (3) stage. The cause of high blood pressure in every period of life in which it occurs is clear, and we see that vascular strain, degeneration and atheroma are the results, and come early or late in accordance with high blood pressure; in those who live always on a uric-acid-free diet they will come very late, perhaps not at all in the first hundred years. But if a patient suffers badly in stage (2) and develops Bright's disease, he will have high blood pressure, arterial degeneration and its results; and diet alone makes the difference between the one extreme and the other. Those suffer most in stage (2) who introduce most in

stage (1), *e.g.*, public school boys from the upper classes; and those suffer most in stage (4) who introduce and retain most in stage (3). Stage (3) is twice as long as stage (1), so that a greater retention is possible. Results in individual cases will vary with such things as digestive power, activity, climate, and exposure to heat and cold; but the rule is the same, and knowing the factors we can foretell the issue.

As regards slighter physiological alterations of the capillary reflux, such as those shown in fig. 38, I advise that the capillary dynamometer and the metronome be used to estimate them, but for well-marked pathological conditions such as acute fever or post-febrile conditions, Bright's disease and diabetes, the point of the finger and mere counting half seconds are sufficient. Still, for accurate comparative work, it is always better to use an instrument giving a constant surface and a measured pressure.

We learn from this chapter that in measuring any circulation condition we of necessity measure the quantity of uric acid in the blood.

Uric acid, as one of my patients aptly puts it, is "the variable resistance in the circulatory system."

CHAPTER VI.

Headache.

The headache which I call "the Uric Acid Headache" is, I believe, the same as migraine, megrim, sick or bilious headache, for an account of the history, symptoms, and relationships of which, we owe so much to Dr. Liveing.

The points about this headache which best serve to distinguish it are:—(1) its periodicity; it occurs once in a week, fortnight, month or longer period, for many years, or for the whole life, tending to be more frequent and severe in spring and early summer (see fig. 4), in women it is associated with the menstrual epoch (see figs. 31 and 32); it is usually worst at those hours in which the excretion of uric acid is normally greatest (see figs. 2 and 3); (2) its duration is generally under twenty-four hours, though in exceptional cases it may last for forty-eight; a patient goes to bed with a more or less severe headache, and wakes free. This short duration is of great diagnostic importance in distinguishing it from the more continuous headaches, such as those due to neuralgia or intracranial disease, which often last for days or weeks with little or no alteration. The uric acid headache is due to the passage of an excess of uric acid through the blood; but apart from organic disease this (uric acid collæmia) can only last a few hours; the uric acid is eventually excreted, and the headache ceases.

The eye symptoms carefully described by Liveing have only affected me occasionally, but have been more marked of late years, when the headaches have been both less frequent and severe than 25 or 30 years ago.

Their most frequent form in myself is that of finding half an object blurred, as the upper or lower half of a picture or the right or left hand side of a page; I have frequently had flickering as of a fortification pattern, or the flashing of light on quickly rippling water, and this more often at the right of the field of vision. However, one of

my children suffered from this headache till cured by diet, and in him the eye symptoms were the rule rather than the exception, so that he himself distinguished a febrile headache, such as that of influenza, by the absence of the eye symptoms.

As noted by Liveing and others the pulse is slow and of high tension (see fig. 44), the surface and extremities are cold, and the temperature even in the axilla subnormal. Some observers have noted pulses of 48 and 52 during the attack (see Fagge's "Medicine," ed. 2, vol. i., p. 784).

The tongue may be clean or slightly furred, the appetite may be fair, but is often irregular, emptiness and ravenous hunger being quickly replaced by a feeling of distension and satiety; in fact, there are signs of dyspepsia, though slight. When the headache is severe there may be nausea or vomiting; but these are generally late symptoms, and are absent or little marked when the headache first comes on.

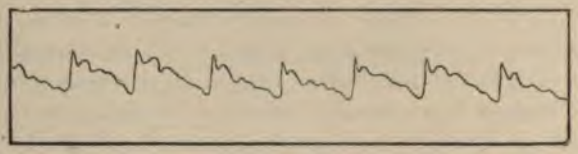

FIG. 44.—PULSE TRACING OF HIGH BLOOD PRESSURE IN A URIC ACID HEADACHE.

The bowels may be regular and the motions natural; but commonly they are a little irregular, either slightly relaxed or slightly constipated.

The urine during the attack is scanty and of high colour and sp. gr.; thus in the attack it may not exceed 30—40 cc. in the hour; after the attack, and especially just as it passes off, it may run up to 100 or 150 cc., or more.

There is often a family history of headache of the same type, or of epilepsy, together with gout and rheumatism, and not very rarely phthisis; chronic nephritis and cerebral hæmorrhage should also, I think, be added to the list of family complaints.

When a headache has a majority of these characteristics well marked the diagnosis is generally easy; but there are several ways in which we can test it.

If the scanty urine of the headache is carefully separated from that passed before and after, it will be found to contain a relative excess of uric acid having a relation to urea varying in different

cases from 1—25 to as much as 1—12 or 1—15, and, generally speaking, the greater the relative excess of uric acid and the greater its absolute excretion per hour, the more severe the headache. With a headache I find ·6 grs. of uric acid per hour and upwards, and when I have removed the headache by acids the excretion falls to ·45 grs. per hour or less; the urinary water undergoing, as before mentioned, an inverse change. Fig. 45 shows the excretion of uric acid and urea on nine consecutive days, on one of which there was a severe headache lasting nearly twenty-four hours. The way in which the uric acid runs up apart from urea is well shown, and it is seen that uric acid was below urea on each of the six days preceding. If we add

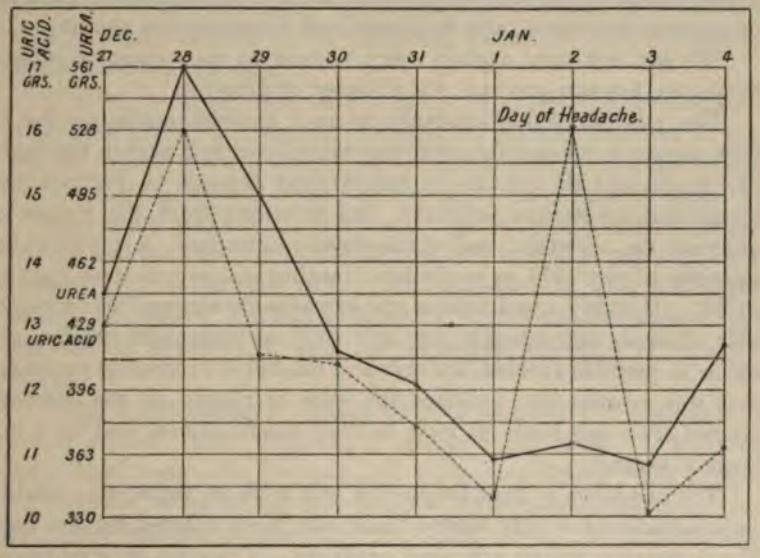

FIG. 45.—CURVES SHOWING THE EXCRETION OF URIC ACID BEFORE, DURING, AND AFTER A HEADACHE.

the amounts by which uric acid fell short of urea on these days it shows that there was a total retention of about 4½ grs., and this is almost exactly the amount by which uric acid exceeded urea on the day of headache. From December 28 to January 1 urea fell steadily, and with this fall no doubt acidity would fall also to a corresponding extent, and the result of this sooner or later would be a plus excretion of urate and headache.

This figure also illustrates what occurs after several good dinners or any other causes increasing introduction as well as formation of uric acid and urea. As urea and acidity rise the patient feels well,

because uric acid is retained; but when they fall, as they must do later, the stored uric acid returns to the blood, and headache, mental depression, or other disorders supervene as the result of indiscretion (see fig. 25, and *Journal of Physiology*, vol. xv., plate x., fig. 4).

All so-called biliousness is practically collæmia, for whatever upsets digestion (as irritating or indigestible food) will cause collæmia. Collæmia produced in other ways, as by fatigue or exposure to cold (fig. 40), will upset the circulation in the stomach, intestines and liver, and so produce dyspepsia and biliousness. Here we have a vicious circle, dyspepsia producing collæmia, or collæmia producing dyspepsia; but if there is no available uric acid the circle is broken; dyspepsia cannot produce collæmia; there is no collæmia to produce or increase dyspepsia, and headache and dyspepsia are absent.

We can not only explain every feature in the causation of this headache, but can produce the disorder at pleasure.

The relation of this headache to gout and rheumatism is due to their common connection with the quantity of uric acid in the body and blood, and its relation to animal food depends on the fact that all animal substances, extracts, and infusions from the tissues of animals, &c., contain, and consequently introduce, a considerable quantity of uric acid or equivalent xanthin compounds (see figs. 25 to 30). If such animal tissues and extracts are stopped while vegetable alkaloids equivalent to uric acid, such as theine and caffeine, are as far as possible avoided, the uric acid headache (migraine) vanishes, and this course also includes the cure of nearly all the diseases treated of in this book, so long as they are functional and have not become organic.

The headache is most frequently met with in those who, having large arteries of supply to the brain, are most affected by the high blood pressure which uric acid produces. There is no anatomical or physiological defect in the sufferers, indeed, they are often intellectually superior to those whose sufferings take another form.

In illustration, I will explain the way in which a slight or severe headache may be caused intentionally or otherwise.

Our problem is to produce a fluctuation in the excretion of uric acid so that 4 or 5 grs. shall be withheld from elimination, shall be retained in some part of the body, be dissolved out and again enter the blood a few hours later, and in passing through it produce high blood pressure, headache and other symptoms.

The largest excretion of uric acid in the twenty-four hours takes place in the alkaline tide of the morning, and one of the simplest ways of producing a fluctuation in excretion is to interfere with the

natural plus excretion of the alkaline tide (see figs. 2, 3, 39 and 40). By giving any of the retentive drugs such as acids, opium, antipyrin, mercury, either before, with, or soon after breakfast, a certain amount of uric acid will be withheld from excretion during the morning. If no more of the drug is given, acidity will fall, either in the afternoon or in the morning of the next day, and then the uric acid retained in the morning will be taken up in the blood and begin to pass out by the kidney, when more or less headache will result.

Another simple way is to take a little opium with or after lunch; this will raise acidity and hinder the uric acid excretion of the early afternoon. Next day there will be some plus excretion of uric acid with slow high tension pulse, headache, &c., in the early alkaline tide of the morning (fig. 35).

It must be understood that I speak of physiological conditions, and of the action of drugs on uric acid in persons who are in good health; where there is functional disturbance, and still more when there is organic disease, conditions are more complex (see chapter v.).

Suppose a patient has dyspepsia and fails to absorb his food, acidity and urea both diminish, a lowered acidity of the urine may continue the whole day, and a plus excretion of uric acid result, until as the gastric conditions improve, food is again absorbed, urea and acidity curves rise, and the excessive excretion of uric acid ceases.

These considerations explain what is seen daily of the effects of diet in preventing or producing a uric acid headache. If a patient has a slight headache, but can still eat a good dinner with a liberal allowance of wine, which may remove his headache and make him feel better because it (especially the wine, see fig. 63) raises acidity and clears the blood of uric acid; this rise will commonly continue next morning, and he will feel bright and well next day also; but if he eats and drinks at this dinner not wisely but too well—if he overpowers gastric digestion—it will cease, and be replaced by nausea and vomiting, urea and acidity will fall, and the uric acid be again in excess in the blood. A severe headache will then occur next morning in place of the well-being and brightness which would have been present if the stomach had not been upset. The second day after a dinner, however, urea and acidity fall, and then the headache will return unless the uric acid be in the meantime removed by a few doses of a salicylate. This is the way in which I ward off the evil effects of a dinner; but the best way of all is to avoid the dinner, or refuse its poisons.

Or supposing there is organic disease of the stomach, such as ulcer or new growth, the fall of urea and acidity will be constant and progressive. If urea falls from 500 grs. to-day gradually to 400, 300, and even 250 grs. in twenty-four hours, the acidity in its relation 1—6·8 would suffer a corresponding diminution, the excretion of uric acid be constantly large, and this would persist until all the stores of uric acid were exhausted, or something occurred to raise the acidity.

Hence it is that a patient dying of wasting disease will excrete for weeks and months an excess of uric acid, and if the urine is examined, uric acid will be found constantly above its normal relation to urea—1—34—this continuing so long as there is any uric acid which can be got into solution.

It is thus that in patients who die slowly of wasting disease we find only erosion of joint cartilages but no urates; we should have found the urates in the urine if we had looked for them in the last few weeks, or attention may be called to the excessive excretion by the occurrence of gravel or calculus, but if the same patient had been killed twelve months ago by acute disease (as pneumonia) we should probably have found them *in situ*, all the erosions filled and plastered with urate, because during the high acidity of the acute fever there was no alkali to wash them out. Sir A. Garrod records ("Gout and Rheumatic Gout," ed. iii., p. 467) an intimate relationship between gout and stone, the one alternating with the other, and this, from my point of view, is easy to explain, for the uric acid which causes gout of the fibrous tissues or joints, when passing out of the body through the kidney causes gravel or stone; when the alkalinity of the blood is low it is driven out of the blood into the joints, causing gout; when the alkalinity is high it is taken up from the joints and fibrous tissues, and passing through the kidney causes gravel, and these two conditions alternate, what is good for the one being bad for the other.

Those who speak of erosion of joints without urate deposit as "rheumatoid," and the same erosion with urates as "gout," are making two diseases out of different stages of the same process (see cases in chapter xvi.).

But to return to headache. If a patient has chronic wasting disease, none of the drugs in our list will stop the plus excretion of uric acid; acids, opium, antipyrin—all will alike be overpowered by the flood of alkali. Or where disease is only functional our drugs may still fail to effect a cure, either because the functions of the stomach are too much upset to permit absorption, or because, after more or less absorption has occurred, the acids are overpowered

by the causes that increase alkalinity. In the case of opium, which raises acidity by acting on the intestines, delaying peristalsis and increasing absorption of acid products of digestion, extensive ulceration may produce so much diarrhœa that only a very large dose of the drug will have effect.

For such conditions almost any single drug, or several combined, will fail to check the plus excretion of uric acid, or to remove the symptoms due to its excess in the blood.

In the above cases of very chronic plus excretion of uric acid the excess is not generally great, and though the presence of some excess in the blood is constant, the quantity may not be enough to produce distinct headache, except occasionally for a few hours. The patient suffers continually from some minor signs of collæmia, of which we shall speak presently.

Speaking generally, however, a uric acid headache, accompanied by a plus excretion of uric acid, can be cured within an hour or an hour and a-half by anything that will raise the acidity of the urine or otherwise stop the plus excretion of uric acid, and, if in any given case we fail, we shall find, if we examine the urine, that we have also failed to raise its acidity, or to stop the plus excretion of uric acid, and similarly the blood granules are undiminished.

The main symptoms and characters of this headache, and first its periodicity, can be explained. The headache being due to a fluctuation in the excretion of uric acid, the first stage of the fluctuation is a retention of urate, and during this process there will be little urate in the blood, and no headache. On the contrary, the signs will be those of absence of uric acid from the blood, just such as are produced in the first stage action of opium, mercury, cocaine, lead, zinc, acids, &c. The patient will feel more than usually cheerful and energetic, and it depends upon the length of time occupied by this process of retention how long an interval will interpose between successive headaches.

On ordinary meat diet I had a headache once in seven to ten days, that is to say, in five to seven days I had then accumulated sufficient uric acid to produce another excessive excretion; on my present diet, I not only form and introduce much less uric acid, but acidity being no longer raised by the acid-forming constituents and acid salts of animal food, but rather kept down by the alkaline salts of fruits and vegetables, nearly all the uric acid I form and introduce is excreted, and only very occasionally, and at long intervals, or after some excess in nitrogenous food, or exposure to cold, do I accumulate enough uric acid to produce a headache as it passes through the blood.

The fact that I do thus occasionally get a headache shows, however, that there has been no anatomical or physiological change, and that enough uric acid in the blood causes recurrence.

The onset of a headache is often preceded by more than usual mental brilliancy and well-being, this corresponding with the fluctuation of uric acid excretion which precedes the attack in nature, just as it does when an attack of headache is produced artificially, and figs. 39 to 41 reveal the exact causation. The same thing has been noticed before the fit of epilepsy, and is probably due to the same cause.

The relation of headache to menstruation is clear, for menstruation is almost always a cause of some little disturbance of function, which often specially affects the digestive organs, so that food is taken badly or badly digested, and exercise is generally deficient. Several of these causes combined produce some failure of nutrition, with a fall of urea and a corresponding fall of acidity, and this is the signal for any retained uric acid to be got into solution and flood the blood. Menstruation is thus commonly accompanied by lowered acidity, plus excretion of uric acid, and the effects of its excess in the blood, such as the slow high tension pulse noted by Sir W. H. Broadbent, and mental depression, and if there is much uric acid in reserve more or less severe headache or an epileptic fit may occur (see figs. 31 and 32).

The reasons why headache is worst at the hours of normal plus excretion of uric acid—that is, in the periods of low acidity after breakfast and lunch—are now, I hope, too obvious to need further mention. As a rule (when the kidneys are normal, and have not had their alkalinity diminished by local inflammation or disease) the five or six grains of uric acid, which occasion a headache by their passage through the blood, are all excreted in a few hours, and the headache subsides. But I have seen cases in which attacks of migraine had suddenly become more frequent, severe and prolonged, and further investigation has revealed that Bright's disease has supervened, and an organic cause of uric acid retention is added to the original functional one (see chapter xiii.).

As regards the causation of the headache, the effect exerted by uric acid on all the vessels of the body, is closely allied to that which, occurring locally, has been supposed to cause the pain. It has been suggested by Du Bois Reymond and others, quoted by Liveing (p. 295 *et seq.*), that the headache is due to irritation of the vasomotor nerves in the region of the cervical sympathetic, giving rise to contraction of vessels in certain areas, followed by dilatation

and congestion. Sir T. Lauder Brunton (*St. Bartholomew's Hospital Reports*, vol. xix., p. 333) supposes that the proximal ends of certain vessels are dilated, while the distal ends are contracted, and that the impact of the blood against the contracted extremity produces pain. I think, however, that the effects of uric acid in obstructing the peripheral vessels and producing high blood pressure, and the effects of this on the intracranial circulation, give us a much better explanation than any more or less hypothetical irritation of the cervical sympathetic.

Taking it for granted, then, that an excess of uric acid in the blood does obstruct the capillaries and cause high blood pressure, the researches of Professor Grashey, which I have quoted in *Brain*, Spring and Summer Numbers, 1893, show that when arterial tension rises above a certain point, the pressure in the closed cavity of the skull becomes so great that the small veins on the convex surface of the brain are compressed and begin to vibrate, the blood stream through them being greatly hindered, and from this more or less stasis and hyperæmia result in the veins and capillaries behind the point of compression, with general excess of pressure in the cranial cavity.

Professor Grashey further suggests that as the cerebro-spinal fluid comes from the blood, this condition of stasis and hyperæmia may increase its quantity, and with it the intracranial pressure.

I believe such a general increase of pressure acting within the unyielding membranes of the brain may account for the pain of headache, in so far as it is bilateral, and that where it is unilateral, or apparently affecting chiefly the distribution of a single nerve, there may be some œdema affecting specially the sheath of that nerve, due to the changes in the circulation, just as the more general increase of cerebro-spinal fluid may be due to it. And this may account for the paralysis or paresis of certain nerves which sometimes occurs contemporaneously with a migraine (see *Lancet*, 1893, vol. ii., p. 139). Stasis or thrombosis which would probably produce œdema and pressure has been actually observed taking place in the vessels of the retina during an attack of megrim (see article by Mr. Stanford Morton, *Ophthalmic Review*, March, 1890).

In the *British Medical Journal*, 1903, vol. i., p. 1020, Dr. J. W. Russell records a case of migraine associated with paralysis of certain muscles of the left eye, the probable explanation of which I have given. Reference is also made to similar cases recorded by previous observers.

We must remember that though fluid pressures are equal in all

connected tubes, the larger the artery contained in the closed box of the skull the greater will be the effect which its dilatation produces on the other contents. Hence those with large arteries at the base of the brain may have headache with a blood pressure of only 130, when others with smaller arteries will only have it at 160 or 180. Certainly some get headache at 130, others not till 180. And a blow, a tumour, or syphilitic thickening of membranes may so diminish the available space within the skull as to make the difference between headache or no headache with a given pressure.

As regards the bilateral headache, Dr. W. Rushton Parker, of Kendal, has reminded me of the fact indicated by Sir Victor Horsley (*British Medical Journal*, 1893, vol. ii., p. 1366) that opening the skull invariably cures the headache of cerebral tumour by relieving pressure, so that the intense headaches of migraine and cerebral tumour may both be due to excessive intracranial pressure.

A rise of blood pressure means an obstruction of capillaries throughout the body, and a deficient circulation which can now be measured in the capillaries of the skin; the brain tissues probably share this deficient circulation; and such minor defects of function as are expressed by mental depression and increase of irritability may be its clinical signs; but if the block in the capillaries increases, and the pressure rises higher, we get an effect on the intracranial circulation differing from that on the rest of the body.

The pressure acting in a closed cavity compresses the veins at their point of entry into the large sinuses, and we get more or less venous hyperæmia and stasis, and eventually increase of cerebro-spinal fluid, and so still further increase of intracranial pressure. The effects thus produced are serious and become pathological, with such symptoms as headache, vertigo, coma, or fits of epilepsy or uræmia. So constant are these results that with many people it is possible to form a fairly accurate estimate of their blood pressure simply from their temper; when this is short, blood pressure is high, when it is calm and placid, blood pressure is distinctly lower; when there is hysteria and excitement, as in women, there is some heart failure in consequence of collæmic obstruction of capillaries (see chapter viii.).

I have noticed in my own case a fact of some interest, namely, that when the pain is severe and situated in the centre of the occiput (? nuchalalgia of Dr. Burnett, see chapter viii.), sitting with the head bent back so that the face looks vertically upwards, will greatly mitigate the throbbing pain, and possibly this position may interfere with the increased pressure of arterial blood corresponding to each

throb. Speaking generally, the vertical position is the only one bearable; when I have an attack I am obliged to sit vertically upright against the back of my bed and slide gradually into the usual recumbent position as the pain moderates. Stooping makes even a slight headache unbearably severe, and the effects of position on intra-arterial pressure suffice to explain these facts, for Marey says: "Dans l'attitude verticale un animal aura donc une pression manométrique plus faible à la carotide que le femorale et surtout que la métatarsienne" ("La Circulation du Sang," p. 192).

In the vertical position gravity is acting against the circulation in the carotid, with the circulation in the femoral, and both the sphygmograph and the arteriometer show similar changes of pressure and diameter in the radial artery, when the arm is raised, horizontal, or hanging down.

The fact that compression of the carotid has often been used to relieve the pain of headache points the same way (see Dr. Liveing, "Megrim and Sick Headache," pp. 376-7).

To diminish fluids for twenty-four to thirty-six hours undoubtedly lowers my blood pressure, and makes a headache so trivial that I can disregard it. It does not alter the excretion of uric acid present in excess in the blood and passing out of the kidneys freely; but it lowers blood pressure by diminishing available fluid. There is no doubt that this lowers blood pressure, as from 140 with headache to 120 with little or none. Of course the results depend on the fluids available in the body. My body fluids are roughly 10 pints, my daily loss 2½ pints, and my daily intake about the same. If I go twenty-four hours without fluid, the loss being continued, they are reduced to 7½ pints. Or again, if I withhold fluids for thirty-six hours I can reduce them to 6½ pints.

In a case of dropsy much more must be done, as you are dealing here with 20 pints in place of 10, and a removal of 5 pints will have a proportionately smaller effect, because the fluid is reduced only by one quarter instead of one half.

If diminishing fluid produces no fall in blood pressure, why do we give cathartics to patients with high blood pressure in danger of cerebral hæmorrhage, &c.?

As a fact one finds that blood pressure of 140-150 with a headache, is reduced by twelve to twenty-four hours' diminution of fluids and some diminution of food to 110 and no headache.

Exercise affects the head pain in accordance with its effect on intra-arterial pressure; the first effect of muscular exertion is to raise blood pressure and make the headache worse; but if it is

continued to the extent of producing general relaxation of the vessels in the muscles, with warm and perspiring skin, this brings about a fall of blood pressure, and the headache departs.

And though part of the fall of blood pressure is, no doubt, due to the increased area of circulation in the muscles, we must not forget that the heat tends to clear up collæmia and so free the capillary circulation and lower the blood pressure.

Vertigo is one of the most interesting results of high blood pressure, and as its causation is probably exactly parallel to that of headache and epilepsy, it throws an important side light on their origin.

Murchison classed vertigo among the disorders associated with lithæmia, and Dr. Buzzard ("On Vertigo of Bulbar Origin," *Lancet*, 1890, vol. i., p. 179) points out that a gouty history is common, and salicylate of soda is useful in treatment, a fact which he explains by reference to my researches on the action of this drug on uric acid.

In so far as vertigo is of "bulbar origin," I take it that it is the exact parallel of uric acid headache or of epilepsy, and that the high blood pressure and consequent increased intra-cranial pressure producing the two latter, may produce also the former; indeed, I have had many cases of vertigo in patients with high blood pressure in which the reduction of pressure has effected great improvement or cure.

Everything said or to be said about the causation and treatment of headache applies also to vertigo.

Dr. Buzzard (previous reference) mentions that these attacks may be followed by a large discharge of colourless urine. Here again is an exact parallel with epilepsy and migraine.

I have myself had one or two attacks of temporary vertigo, coming in the morning when blood pressure is generally high and uric acid in temporary excess in the blood. I looked upon it as a variation of migraine, with which it corresponded as regards time of onset and symptoms.

Dr. Buzzard suggests that this vertigo may be due to an affection of the bulb near the origin of the auditory nerve, and signs are not wanting (with the headache, mental depression, and other symptoms of collæmia) of some slight functional derangement in this region, for I have pointed out (*Brain*, 1891, and elsewhere) that a certain amount of aphasia with forgetfulness of names, &c., is very commonly associated, and Dr. Bastian (*Lancet*, 1890, vol. i., p. 1164) says: "Thus, when there is a slight lowering of functional activity in the auditory centre we have produced a slight amnesia, with

forgetfulness of names of persons and things, the centre not being sufficiently active in this condition to respond to some volitional and associational incitations," and I would add that in collæmia ot a few other centres on which activity of mind and body depend in a similar condition of lowered functional activity.

Iow, a certain amount of this amnesia is one of the most common paniments of the headache and mental depression due to col- and the centre which, according to Dr. Bastian, is affected be far from that to which Dr. Buzzard attributes vertigo.

matter of practical interest I may say I have several times le to cure vertigo merely by cutting down fluids, or in other oth food and fluids, as advised later in the treatment of he e.

Speaking of similar conditions, Sir W. H. Broadbent says ("The Pulse," p. 249): "There may, for example, be a fugitive aphasia or amblyopia or hemiopia, which are easily explained by stasis or ischæmia in certain vascular areas, but incomprehensible as the results of a poison circulating everywhere through the brain." My version would be that uric acid, by its effects on the vessels, produces the "stasis or ischæmia," which causes the symptoms in these and similar conditions. The whole brain, and for that matter the whole body, is affected in much the same way, but certain parts, possibly owing to local conditions of anatomy, function or nutrition, are specially affected and give rise to special symptoms.

An interesting case of periodic stammering, having probably an identical pathology with several of the above-mentioned conditions, is recorded in the *British Medical Journal*, 1893, vol. ii., p. 1311, and I have often noticed that stammerers are decidedly worse when they are over fatigued or a little out of sorts, conditions equivalent to the presence of more or less collæmia.

Hence it is only people with these anatomical or physiological peculiarities who suffer from headache, epilepsy, or vertigo, as the effects of collæmia, while others with as much uric acid may almost entirely escape. As regards migraine, I have suggested (*Brain*, 1893, p. 250) that the possession of large arteries of supply may render some more liable than others to suffer from the intracranial effects of high blood pressure; this in part accounting for the fact that migraine is more common among those who work with their brains than among those who work with their muscles.

The relation of this headache to gout is interesting and obvious, and there are many recorded cases in which severe headaches of this kind unexpectedly cleared up on the supervention of an attack of gout.

Nothing can be more simple than the explanation. The urate cannot be in two places at once, and when local injury, plus rise of acidity, causes its precipitation on the toe joint, the blood is more or less quickly cleared of the previous excess. The headache, slow high tension pulse, cold surface and extremities, mental depression and scanty urine therefore vanish, and pain and inflammation in one or more joints, with low tension pulse, free capillaries, and a certain amount of fever replace them; immediately, in spite of some pain, the mental condition is more placid and the urine more profuse.

So far I have found that patients generally have headaches early in life and gout later, but not the two together, though patients with well-marked gout may occasionally have severe headaches.

The headache occurs when conditions tending to the plus excretion of uric acid predominate; the gout with conditions tending to its retention and accumulation. Once urates are extensively deposited in joints they tend to accumulate, so that the blood is kept pretty free, so long as there is no marked and continued fall of acidity. But when the patient becomes old and feeble, acidity falls, and the process is reversed; there is no gout, but an excessive excretion of urate, and the signs of collæmia, *i.e.*, headache, depression, slow pulse, &c., are severe and well marked. And it is not difficult to imitate nature, and produce either gouty arthritis or collæmia and headache.

Opinions have been expressed on the use of setons in the neck as a cure for migraine,* and although I noted that they seemed useful I did not see the explanation of their action. But one day when I was talking with Dr. Dawtrey Drewitt about some of the phenomena of the uric acid filter, as mentioned on p. 170, I referred to these facts and to the way in which a gout of a joint or of the skin (eczema or psoriasis) may alternate with such collæmic diseases as headache, epilepsy or mental depression, remarking that practically any local irritation might act as a uric acid filter with regard to the rest of the body and the blood. Dr. Drewitt, who had had experience of the use of setons in the epilepsy of children, suggested that it was probably in this way that setons act, keeping the blood clear of uric acid and preventing for a time the onset of the attack. If this is so, we have in the use of setons for migraine and epilepsy a repetition of what occurs in nature, *e.g.*, when a furious attack of gout in the toe replaces headache, or mental depression. Perhaps as the reverse of this when such a local irritation is suddenly

* See *British Medical Journal*, 1902, vol. i., pp. 587, 961 and 1025.

healed, collæmic disease may return, and hence the observation of the ancients that the cure of a discharging ulcer, an eczema or psoriasis, may be the signal for the onset of headache, mental depression, albuminuria or glycosuria. I know several patients who are kept alive and to some extent out of danger by a discharging sore; and in such cases it would be unwise to try and heal it. It is probably both a natural seton and an outlet for some of their uric acid.

Depending as this headache appears to do on the intracranial effects of high blood pressure, it seems evident that anything lowering blood pressure will make the headache less frequent and severe.

Blood pressure varies, as we have seen, chiefly with three factors: (1) the obstruction of the capillaries, (2) the power of the left ventricle of the heart to overcome the intra-arterial pressure at each systole, and (3) the quantity of fluids in the vascular system.

Therefore, blood pressure can be reduced by three things (1) anything that will free the capillaries from globular or colloid urates; (2) anything that will weaken the left ventricle and prevent it discharging the whole of its contents into the aorta at each systole; and (3) anything that diminishes the fluids in or available for the vascular system.

It is obvious that not only will all drugs and diet, which reduce the uric acid passing into the blood or directly clear it out of the blood, do good by freeing the capillary circulation, but drugs or conditions which tend to weaken the left ventricle of the heart will also prevent or relieve headache by reducing blood pressure. And the drugs classed as depressomotors may, I think, thus reduce blood pressure, partly by reducing the power of the muscles in the walls of the arterioles, and partly by a similar depression of the heart muscle. Such drugs as tobacco, ipecacuanha and antimony may very probably act in this way, and Dr. Liveing records (prev. ref.) that some of them have been used with good effect in migraine.

Further, it is known that as sufferers from this headache begin to grow old, their attacks may become less frequent and severe, or may cease. Such people, I think, have some relative weakness of the heart, so that the pressure necessary to produce migraine can no longer be maintained.

I shall probably be reminded by pathologists that the wall of the left ventricle grows thicker with advancing age; this doubtless shows that the heart has often more to do at 65 than at 35, but not that it does it better.

A case in which I was much interested furnished what was probably an instance of this. After years of periodical suffering, in extreme old age, with marked signs of debility, the headache disappeared, but was replaced by more or less periodical attacks of palpitation, that is to say, whenever there was collæmia and the capillaries were obstructed, the heart failed and palpitated and could not keep up the pressure (see fig. 37). Here there was no doubt about an excessive excretion of uric acid, as the patient was greatly troubled with uric acid gravel.

I have several times seen cases in which migraine has been treated more or less decidedly with antipyrin, and has remained absent for some little time; in one an irregularity in the action of the heart dated from a large dose of antipyrin taken for headache; and in one or two others I have found fairly marked signs of cardiac failure, which there was nothing but the antipyrin to explain. We must not lose sight of the possibility that antipyrin, if pushed, may weaken the heart and thus keep off migraine for some considerable time.

A patient who has been a sufferer from paroxysmal headache for some forty years, told me that recently after an attack of influenza she was treated for weakness of the heart, and while this continued the headache was absent, but has since returned; and to-day her blood pressure is 140, and her capillary reflux 7—8 (see also Case recorded on p. 140).

When, on the other hand, a migraine, habitual for many years of life, suddenly becomes more frequent and severe, make sure that you have not to deal with the onset of nephritis; I have several times been misled in this way till I examined the urine. Nephritis (as we shall see in chapter xiii.) generally means chronic collæmia, hence, contemporaneously with its onset, the uric acid headache will become more frequent and severe, will be more difficult to treat and less amenable to drugs and diet. As will appear in chapter xiii., I regard collæmia as the chief contributing cause of the nephritis, though where this complication has supervened it will make the blood condition worse. Dr. Gee in a clinical lecture (*St. Bartholomew's Hospital Journal*, June, 1897), describes a form of chronic headache related to gout and to migraine, which he says is "commonest in men in adult life whose energies are just beginning to fail." This is exactly the time of life at which migraine tends to pass into Morbus Brightii, and there may be for a time more or less chronic collæmia. It is most often seen in men because their hearts are stronger and can keep up the pressure for a longer time; when they

get still older their hearts fail like those of women, and then (as in the case previously mentioned), they get palpitation instead of headache.

If there is no sign of Bright's disease look for morbus cordis, which may intensify the bad effects of uric acid on the circulation, or failing this, inquire for recent severe illness, new growth, shock, or other cause of failing nutrition.

I had an illustration of this in the case of a patient with all the signs of chronic collæmia. I could find no morbus cordis, though she had the cardiac signs of collæmia; I therefore suspected the kidneys, but there was no albumen. I could not account for the symptoms, but a few months later it became evident that she was suffering from cancer of the œsophagus, and this had doubtless caused low nutrition and collæmia.

I mention this because it is necessary to bear in mind that the uric acid headache, as also epilepsy and mental depression, associated only with functional disturbance are a very different matter, both as to prognosis and treatment, from the same troubles when associated with organic disease.

The functional trouble is rather a warning or danger signal—a sign of temporary high blood pressure that something must be done to relieve—it is hardly a sign of actual disease, and with a little attention to diet may be permanently relieved, especially in the young.

The migraine associated with organic disease is more serious, it may be a later stage of functional trouble, or the organic disease (nephritis, morbus cordis, arterial degeneration, neuritis, &c.) may be a co-result of more or less chronic and unrelieved collæmia; but, whatever its exact origin, the treatment is that of the organic disease, and if we can relieve this the migraine will improve.

Success is however more difficult to attain, and unless functional and organic cases are clearly distinguished, which cannot be done without great care, the treatment I am now suggesting may get less credit than is its due.

Diagnosis.—When there is a paroxysmal headache lasting from six to thirty-six hours, which has recurred every seven to ten or thirty days for many years, accompanied by a slow high tension pulse, and scanty excretion of urine, with marked coldness of the skin and extremities, and slow capillary reflux, which in a female frequently occurs in relation to the menstrual epoch, or in a male is apt to follow the day after some unaccustomed muscular exertion, or sexual intercourse, there can hardly be much doubt about the diagnosis.

Organic headaches sometimes resemble migraine; but the paroxysmal history is absent, and when a headache has lasted more than thirty-six, and certainly when more than forty-eight hours, migraine should be considered very doubtful.

I have seen at least one case of hemicrania or migraine where the trouble was organic and not due to uric acid; here there was a complete absence of the paroxysmal history, and the pain lasted for several days; one such case was relieved by large doses of iodide of potassium, but there was no specific history.

I have seen this patient *recently*, and found a capillary reflux 5 to 6 and blood pressure 110, but these conditions of the circulation are never present during an attack of uric acid headache, and only rarely present in sufferers from this disease even between attacks.

There can be little doubt that he has some local cause of increased intracranial pressure, and again he was relieved by large doses of iodide.

In doubtful cases diagnosis must depend on conditions present in the circulation, and if necessary on the quantity of uric acid in the blood and urine, and these will always suffice to distinguish the true uric acid headache from the pain of eye strain or of local conditions about the nose or frontal sinuses, or other organic disease.

The indications for treatment are—(*a*) *during the attack* to clear uric acid out of the blood as quickly as possible by means of any of the drugs with this effect. One of the best ways is to take calomel, finely divided with sugar of milk, say gr. $\frac{1}{8}$ every half hour for two or three doses. If there is nausea or vomiting put a mustard leaf on the epigastrium for twenty to thirty minutes before using drugs by mouth. A small injection of morphine may relieve the head where there is deficient gastric absorption, and when the stomach is much upset this is often the only thing that will act, or temporary relief may be obtained by compressing the carotids. Either the calomel or the morphine may be followed by a short course of salicylate of soda to clear out the retained uric acid. (*b*) *Between attacks*, diminish the amount of uric acid introduced in food by avoiding animal foods, soups and extracts which are rich in it (see chapter xvii.), also strong coffee, tea, and vegetables rich in alkaloids, as the pulses (peas, beans, lentils, pea-nuts), mushrooms and asparagus, and clear out any accumulations of uric acid already existing, which may be best accomplished by a course, or several courses, of salicylate at intervals. It is necessary to drop all animal food except milk and cheese; and milk, bread stuffs, and cereal foods with cheese must be increased so far as is necessary to replace the animal food.

If this is done properly there need be no fall of urea, which I take as the guide of nutrition, and try to keep between 3 and 3½ grs. per pound of body weight per day for an adult.

In many cases change of diet is all that is necessary, and many such are reported to me. Dr. Logan, of Ecclefechan, N.B., mentions several. In some there were "bilious attacks, with headache, sickness, rigors, and diarrhœa," in others headache and sickness of many years' standing, all practically cured by diet. Of one of these he says that when out at dinner or a dance, "if she takes a meat dish to save being remarkable she always suffers headache and depression within two days," the exact parallel of my own experiences (similar cases are also recorded by Dr. Eskridge and Dr. Ferguson. See references in chapter vii.).

I have found this headache so constantly associated with a large excretion of uric acid in the urine that I have practically given up examining or recording the urine excretion, trusting entirely to the very definite circulation changes, with an occasional estimation of the blood granules; or have only examined the urine now and then in response to a request by those who have sent me cases.

Thus Dr. Fiddian, of Cardiff, kindly had the urine of an attack collected, and found a relation of uric acid to urea of 1—18. He sent the patient to me, and I found the blood pressure between attacks was 120, in spite of some quick pulse (? cardiac failure) and the capillary reflux was 6 to 7 decidedly slow; the apex of the heart was slightly displaced to the left, and the second sound was loud.

And this reminds me to say that sufferers from this headache generally have too high a blood pressure and too slow a capillary reflux even between attacks, and that their circulation signs alter in the direction of normal, in six to nine or twelve months as the diet is persevered with.

Thus a patient with a blood pressure of 170—180 in an attack will have a blood pressure of 140 say between attacks: but 140—150 is the highest pressure I ever get, so that the pressure required to produce an attack varies with the individual.

Blood pressure also no doubt varies with atmospheric pressure, and Dr. J. Cuthbertson Walker of Mevagissey, St. Austell, Cornwall, pointed out to me that his headaches had been more frequent living on sea-level in Cornwall than previously in the highlands of Scotland.

Now a rise of blood pressure equal to 20 or 30 mm. of mercury suffices to produce a headache in myself, and since atmospheric pressure falls 1 inch = 25·3 mm. of mercury in 900 feet, it follows that a rise of 900 or 1,000 feet would be required to do away with

that headache; while a rise of say 100 or 200 feet might sensibly diminish it.

I have heard from Dr. W. Young, of Wellington, N.Z., the following very interesting history:—

He noticed while on the voyage to New Zealand that one of his fellow-passengers took no meat, and found he had abstained from it for eight years for humanitarian reasons.

Dr. Young then enquired as to the effects, if any, of the change of diet, and was told that this had been much better of late years than previously, and that he had given up alcohol, of which he had before taken freely.

While a meat eater he had been subject to bilious attacks with severe headache, coming sometimes weekly, but since the change of diet the attacks gradually diminished, and are at present quite rare.

Dr. Young adds that he seems well nourished, but that he takes some animal food in the shape of eggs and milk. My impression is that if he stopped the eggs he would remain well nourished, and have no bilious attacks. I see that Dr. Herringham, *St. Bartholomew's Hospital Journal*, 1897, vol. i., p. 99, finds that abstinence from meat cures migraine, though he objects as much as ever to the theory that explains its action: but he refrains from tendering a better explanation, and falls back on useless generalities about assimilation. It certainly seems to me that when the investigation of any disease has arrived at such a stage that it can be produced at pleasure by swallowing known quantities of definite chemical substances (xanthin or uric acid), and certain cure can be effected by leaving these substances out of the diet list, there is not much room for further theory of causation.

I must note two interesting articles by Prof. Pierre Fauvel, "Les Idees de Haig sur L'Acide Urique et les Maladies dont il est la cause," and "Influence du Régime Alimentaire sur L'Acide Urique" (*Archives Medicales D'Angers*, 1905).

On page 558 of the first of these he says: "These facts have long appeared to me to be almost inexplicable, and it is the theory of Haig alone that has given me the key to their explanation." Again, "the observations I have been able to make on myself and some of those round me, confirm absolutely the theory of Haig with regard to migraine. The maladies due to collæmia, from which results a raised arterial tension in the skull yield almost immediately to the action of precipitants of the most diverse kinds, such as antipyrin, salts of iron, phosphoric acid, caffeine and camomile, and almost immediately there is produced diuresis in succession to the diminished urine of the attack."

"Now we know that the diuretics are the precipitants, and that the abundant urine passed in these conditions contains little uric acid. It is thus by their action on uric acid, the only property which they have in common, that these different drugs produce their effects. On the other hand, like Haig, I have been able by taking during several days foods rich in xanthin together with precipitants, to diminish the excretion of uric acid, and to produce in myself a sufficient stock to bring about at pleasure—an attack of migraine, when I administered some doses of solvent sufficient to bring about the necessary collæmia."

Prof. Fauvel in these articles confirms in every detail the main points of my researches with regard to migraine.

As regards treatment by drugs, we must not forget the action of bicarbonate of soda previously referred to, for it certainly sometimes relieves headache and depression in a very marked manner, and probably does this not by diminishing uric acid in the blood, but by altering its solubility, and perhaps preventing it from assuming the colloidal form; that is to say, by carrying the reaction of the blood to the alkaline side of the collæmic point (see chapter v.).

Two or three bicarbonate of soda lozenges will often make the difference between the presence or absence of slight headache and depression, and are specially likely to act well in warm weather in summer just at the time when salicylates do not act well. The high alkalinity of the blood met with in warm weather is favourable to the action of the bicarbonate, unfavourable to that of the salicylate, and we know that the effects of salicylates on blood pressure depend on the alkalinity of the blood, the quantity of uric acid they meet with, and probably upon the compound they form with it.

It is common experience among migraine sufferers that on waking with a headache in the morning the best thing to do is to dispense with breakfast, and perhaps food through the day.

This has some advantages and some interesting effects: (1) it leaves the gastro-intestinal digestion free to get its house in order without fresh duties when its circulation is slow and obstructed.

(2) The effect of starvation is low and falling urea (see "Diet and Food," ed. vi., fig. 1), and with falling urea goes falling acidity, so that the alkalinity of the blood may be increased and the solubility of the colloid uric acid improved, as in the case of bicarbonate of soda.

(3) The effect of falling urea is a fall in nutrition and muscular power (see "Diet and Food," prev. ref.), which means sooner or later a fall of blood pressure. If the patient takes no fluid as well

as no food (and there is never any thirst in these collæmic conditions, because the water cannot get out of the blood through the obstructed capillaries of the kidney), this will also tend to reduce blood pressure.

Hence, after 12 to 24 or 36 hours of more or less complete starvation there is a fall of blood pressure, and the headache ceases. Not because the large excretion of uric acid has ceased, as falling urea and falling acidity favour the excretion, but because the pressure falls from diminished food and fluid. And it is an important advantage of the treatment by abstention from food and fluids as compared with that by retentive drugs (mercury, morphine, &c.), that the uric acid passes out freely, and is not stored.

The fall of blood pressure may be due partly to the better solubility of uric acid in an increase of alkali, as in the case of bicarbonate of soda, and partly to the general muscular debility which prevents the heart from keeping up the blood pressure, and also to the diminished quantity of blood. And the fall of blood pressure is the relief or cure of the head pain.

Dr. W. J. Tyson, of Philadelphia, has observed (*British Medical Journal*, 1899, vol. ii., p. 441) that a patient while taking a quart of Vichy water daily was free from migraine, but on stopping this the attacks returned.

The result here was not due to diminished fluid, but might be due to the solvent (this dose would be equal to about 90 grains of sodii bicarb. in the day) clearing up the collæmia and diminishing or dissolving the granules, as in Dr. Mordhorst's experiments. It would also equalise the excretion throughout the 24 hours, making the capillary reflux curves into nearly straight lines (see fig. 41) and preventing retention and fluctuations which are the great precipitating causes of headache.

In my own experience a small dose of sodii bicarb. has sometimes made a headache worse, while a small dose of an acid has relieved; yet I have been well with low acidity and a large excretion of uric acid, and then a little acid has appeared to produce a temporary headache.

I believe there is what I have called a collæmic point; that is, a point at which the alkalinity of the blood is insufficient to hold its uric acid in complete solution, and this is more or less thrown out in bulky colloid granules (collæmia); an increase of alkali may cause re-solution of these granules and clear up the collæmia, this being accompanied by no diminution, but rather by an increase in the excretion of uric acid in the urine; but if the increase of alkali dissolves

out a quantity of uric acid from the tissues and organs, the uric acid may again be present in the blood in quantity beyond what the alkali can hold in complete solution, and the collæmia and high blood pressure will return.

The collæmic point is therefore not a definite point as regards alkalinity, but is a definite ratio between the alkali present and the uric acid present.

The explanation of Dr. Tyson's observation may be that 90 grains of sodii bicarb. generally suffice to hold in solution the uric acid to be met with in cases of migraine: but I have several times given citrate of potash to cases of Bright's disease, to the extent of rendering the urine almost constantly alkaline, and yet the blood pressure has not fallen, it has either remained constant or has slightly risen. Here we may perhaps conclude that the uric acid was present in the blood in such quantities that the greatest amount of alkali introduced did not suffice to dissolve the collæmia (see cases in chapter xiii.).

A relatively small dose of alkali will hold all my uric acid in solution; but in persons full of urates the largest amount of alkali that can pass into the blood will not suffice to do this, and collæmia, slow capillary reflux, and high blood pressure will continue.

An acid acts by causing retention of the colloid granules, *i.e.*, by giving rise to a deposit or retention, which acts as a uric acid filter, in the liver and spleen and other organs the alkalinity of which the acid diminishes; this is accompanied by a diminished excretion of uric acid in the urine, and a fall of blood pressure, because the blood is cleared of colloid granules, and the excretion in the urine thus reveals how a drug is acting, whether by dissolving collæmia, or by causing retention and so clearing the blood.

One thing is certain, that to abstain from food and drink for 12 to 24 or 48 hours cures a headache; and when the headache ceases the blood pressure has fallen say from 150 with the headache to 100 or 110 after the starvation, and there is a diminished excretion of urea and of acid in the urine; yet uric acid, far from being retained, is being still excreted in considerable excess of its normal relation to urea, so that we have cured the headache while eliminating the uric acid, and have not been retaining a store for some other day.

To attain this desirable result I adopt the following rules:—

(1) When the headache begins abstain from food and drink.

(2) If after missing a meal or two the stomach improves and there is decided appetite, take a few plain dry biscuits and a bit of simple fruit (apple), eating little.

(3) Continue this for about 24 hours, increasing the quantities if appetite improves; but never eating a full meal; often taking only 4—5 ozs. of biscuits and about the same quantity of fruit in the 24 hours (this being modified starvation, about 1-6th or 1-7th of a full day's food).

(4) If at the end of 24 to 36 hours the blood pressure has fallen and the headache gone (weak people will require less, and strong people more starvation) gradually return to fluids and ordinary diet.

(5) During such starvation keep quiet in bed or on a couch, and do not as a rule carry on any ordinary work or occupation, as the object of the treatment is to lower blood pressure by diminishing the quantity of blood. After sufferers have tried the treatment once or twice, they will soon learn how much they can do, and may be able to begin sedentary work as soon as the pain moderates.

This headache can be relieved by (1) anything that diminishes the pressure inside the skull (compression of carotid, &c.); (2) anything that diminishes blood pressure generally, as (*a*) clearing blood of uric acid, (*b*) diminishing the fluids in the body, (*c*) diminishing the power of the heart.

It can be prevented by a diet which keeps excess of uric acid out of the body, and thus diminishes blood pressure. And it was this fact of relief and cure by diet that originated my research.

CHAPTER VII.

Epilepsy, Convulsions, and Hysteria.

The probable mode of production of the uric acid headache applies equally to the causation of its near relative, epilepsy.

Du Bois Reymond, whose vasomotor explanation of migraine has been quoted, speaks of epilepsy thus: "Singularly enough, if Kussmaul and Tenner's doctrine is right, which places the origin of many epileptic seizures in a spasmodic constriction of all the arteries of the head, then my migraine would be distinguished from this kind of epilepsy less by the nature of the disturbance which prevails in it, than by its degree and extent" (quoted by Liveing, "Megrim and Sick Headache," p. 300). Dr. Liveing remarks, in speaking of epilepsy (p. 205), "This is doubtless the particular neurosis which exhibits the closest connection with megrim, both in the occasional replacement of the one affection by the other, and also in the occurrence of cases of a character intermediate between the two."

These views in Dr. Liveing's work set me to look for a uric acid fluctuation in epilepsy similar to that of headache, and my results in one of the first cases I investigated with sufficient care were published in the *Neurologisches Centralblatt*, March, 1888. They showed that in the seven hours preceding the fits uric acid excretion was small, having a relation to urea of only 1 to 50, in spite of the fact that these hours included the alkaline tide after breakfast, when excretion should normally have been large; and just as in the uric acid headache, the uric acid thus retained in what should have been the alkaline tide traversed the blood later in the day, and produced the fits (see fig. 40). The uric acid excretion rose with each set of fits and fell in the interval, and with the most severe fits which occurred in the early morning hours of the following day the uric acid rose very high above urea, having the relation to it of 1 to 20, and when the fits finally ceased returned nearly to normal (level of formation) 1 to 33.

Here is a series of epileptic fits corresponding to a headache; like it preceded by a minus excretion of uric acid, in both cases accompanied by feelings of well-being and mental brilliancy (due to absence of uric acid from the blood); like it also accompanied by excessive excretion of uric acid to a considerable extent proportional to the severity of the fits; and like it also in that when the fits cease, excretion of uric acid falls to the level of formation; the plus excretion during the fits balancing the minus excretion that preceded them.

If I had had no previous experience of the uric acid headache, if I had not known that I could produce or remove it by influencing uric acid, I might have drawn a different and, I believe, less correct conclusion as to the causation of some of the fits of epilepsy. I have elsewhere quoted from Dr. Ross ("Diseases of the Nervous System," ed. i., vol. ii., p. 916), notes of a case which show that epileptic fits may be preceded by the same feelings of happiness, well-being and mental brilliancy observable in the case of headache —symptoms due to the same cause, and contemporaneous with a minus excretion of uric acid in the urine, its relative absence from the blood, and a free circulation in the tissues.

My observation that fits are preceded by diminished excretion of uric acid has been confirmed by Krainsky, of Cracow, who finds the phenomenon so constant that attacks can be predicted from the diminished excretion of uric acid in the urine (see *British Medical Journal* "Epitome," 1898, vol. ii., p. 77, and "Mental Affections," by Dr. J. Macpherson, Macmillan, London, 1899, p. 331).

In the "Epitome" of the *British Medical Journal*, 1905, vol. i., p. 29, there is a record of some investigations of the urine of epilepsy in which increase of uric acid and diminution of urea is observed. Diminished absorption of oxygen by the hæmoglobin and of the activity of reduction in the tissues are noted. This doubtless is the result of defective circulation in the lungs and tissues.

The late Dr. A. Sangster reminded me that George Eliot suffered from migraine, and eventually died with chronic morbus Brightii (its natural ending), and that she was accustomed to say, "I am dangerously well to-day," alluding to the well-being preceding headache.

Epilepsy resembles uric acid headache also in the excessive excretion of uric acid and mental depression, and in the subnormal surface temperature (also due to uric acid). In both the pulse may be slow and faltering, as it often is when the tension is high (see also M. Ch. Féré, *Progrès Médical*, vol. i., 1889). Both develop early

in life and last for years, both are periodical, a character common to other functional disturbances produced by uric acid. Both are common in members of the same family, or may affect the same patient alternately.

Both bear identical relations to menstruation (figs. 31 and 32) or to fatigue in both sexes (figs. 46 and 47). Fatigue will frequently precipitate an attack of either in sufferers, and fatigue causes the passage of an excess of uric acid through the blood.

Among drugs the action of acids, nitrites, opium, iron, and quinine is almost parallel in the two disorders.

Both bear identical relations to dyspepsia, ingestion of indigestible food, or other causes of functional disturbance producing collæmia.

The parallel between the two neuroses previously noted by Liveing and others could hardly be more complete; and my researches reveal the nature of the relationship of these functional disturbances to gout, so often suspected by previous observers.

Since I discovered that there was a fluctuation in the excretion of uric acid with the fits of epilepsy just as with the attacks of migraine, I have investigated all possible cases of epilepsy; and though I have only been able to estimate the uric acid excretion in comparatively few, in the great majority I have found more or less well marked signs of a uric acid fluctuation corresponding with the attacks, such as profuse urine before or after the fits, or both, scanty urine at the time, and evidence of slow high tension pulse with mental depression or dulness immediately beforehand. Several of these cases had only slight fits with momentary unconsciousness, and the urine of these never showed any uric acid fluctuation, probably because the plus excretion lasted a very short time, and the amount of urine already in the bladder overshadowed it.

Once, however, a case which had previously with slight fits yielded only negative results, had a severe fit with insensibility lasting for twenty minutes. Directly afterwards I obtained some urine. It soon became cloudy with a pale sediment resembling mucus, but observation revealed that this was falling through the fluid and collecting at the bottom of the glass.

The urine being scarcely cold, I examined this under the microscope, and found that it consisted of colourless lozenges of uric acid. On estimating I found that it contained a very great excess of uric acid, its relation to urea being 1—17. Here a case which gave no visible reaction with slight fits, gave a marked reaction when a severe fit occurred, so that again the excess of uric acid was proportional to the severity.

When the fits give no precedent warning, it is difficult to separate the urine excreted during the fit: it is almost impossible to prevent an admixture of before and during, or after and during, which, as in the case of headache, gave me for a long time negative results. When the importance of this is realised, it is easy in headache to separate the corresponding urine; but in epilepsy it is always difficult, sometimes impossible. In the case narrated in the *Neurologisches Centralblatt* the urine was drawn at the end of each fit, and in some cases at the beginning also, but even then there was admixture of the excretion with that of attacks and intervals.

I give an illustration. B. B., female, aged 20. Fits began at 12 years old. Longest free time, one month; has had seven or eight in twenty-four hours; generally at night or early morning. Worse at catamenial period; but has them also between the periods. Father no gout or rheumatism; used to have "bilious headache." Mother suffers from headache, &c. Maternal aunt the same. One brother and sister both subject to headaches; the sister about once a week, no fits.

Does not know when fits are coming.

Bites her tongue in the fits.

Scarlet fever at 11 years of age.

Measles and whooping-cough as a child.

Bad fits three days ago. Catamenia present.

Recent scar on right side of tongue.

Fifteen days later a fit at 2 a.m.

Urine was saved in two lots—(1) that passed at midnight before the fit, (2) passed a quarter of an hour after the fit at 2.15 a.m. No. 1 was 188 cc. and showed a relative excretion of uric acid to urea of 1 to 34; No. 2 was 97 cc. and gave a relation of 1 to 41. There was, therefore, relatively less uric acid in the period (two and a quarter hours), in which the fit took place; but it will be seen that the separation was anything but satisfactory; No. 2 was obviously made up of the minus excretion before the fit, as well as the plus during, and the minus far outweighed in time and quantity the plus.

Even a few positive results must far outweigh such negative results, even if one had not the parallel case of headache to argue from. I have got patients to pass water every hour of the waking day, and when a fit occurred there was never very much water in the bladder; in some cases there might be almost none at the beginning of a fit, and so the urine excreted during the fit would be obtained pretty pure.

Drs. C. A. Herter and E. E. Smith, who have made some re-

searches on the relation of epilepsy to the excretion of uric acid, with a view of testing my results,* have not, it seems to me, paid sufficient attention to the question of separation.

The smallest amount of urine examined in their tables is 134 cc., and this not at the time of an attack of *grand mal*. All the amounts estimated at the time of an attack of *grand mal* were larger.

Now the amount of urine excreted in an ordinary *grand mal* attack, lasting, including the stupor following the fit, 20 to 30 minutes could not be much more than 30 cc.; therefore, even in the most favourable circumstances, the urine of an attack was mixed with two volumes of urine excreted before or after it, and no excess of uric acid could be expected.

Even in the case of the uric acid headache, the excretion of the whole day may show minus uric acid, while if the urine of the attack is carefully separated, it shows plus corresponding to the hours of headache (see *Journal of Physiology*, vol. xiii.). In my case of epilepsy, published in the *Neurologisches Centralblatt*, to which these authors refer, the urine of each fit was carefully separated; and I pointed out that when the urine of the fits was mixed with that before and after them, the uric acid was normal, while the urine secreted during the fits showed a great excess.

It is useless to examine 150 to 500 cc. of urine, when that excreted during the fit could not possibly exceed 20 or 30 cc.

The authors say again, on p. 234: "The latter [that is, urine passed immediately after seizures] are apt to show a higher uric acid ratio than the urines passed just before seizures; very often, however, the ratio is one that belongs within the limits of health."

This is my result diluted, and as the quantities are not given there is nothing to show that the urine just before was not the urine of two to three hours before, *i.e.*, a mixture; or that the urine passed after the fit really corresponded only to the excretion of the fit.

Again they say: "The excess of uric acid observed in epilepsy cannot reasonably be construed as the cause of the seizures." They acknowledge that there is an excess, but differ from me as to the relation of cause and effect, though we shall see they now incline to attribute more power to uric acid.

In *petit mal*, however, they found a distinct relation between the excretion of uric acid and the cause of the seizures, and treatment by milk diet greatly reduced the frequency (prev. ref., p. 239).

I should expect this; as I have not limited myself to *grand mal*,

* See *New York Medical Journal*, August, 1892.

but suggest that *petit mal*, hystero-epilepsy, and hysteria are all similarly related to uric acid.

Where attacks of *petit mal* are frequent, I predict a continuous plus excretion of urates; but, as I have often proved, it is useless to look for a urate reaction in a single short attack, as the separation of urine can never be sufficiently accurate.

If Herter and Smith separate the urine of *grand mal* cases with greater precision, I have no doubt that they will get urate reactions similar to mine, and if they will also treat *grand mal* to the same diet as *petit mal*, they will doubtless attain the satisfactory results of others.

The observations of these authors on the relationship of the fits to intestinal putrefaction are of extreme interest in supplying an illustration of a point I had previously noticed. In *St. Bartholomew's Hospital Reports*, vol. xxiv., p. 226, I remarked: "Salicylates may fail to be absorbed for a time from gastric irritation or other causes, and I had a remarkable instance of this in a case of epilepsy which I was treating with this drug. On several occasions the urine gave no reaction with perchloride of iron during the fits, though on some occasions there was probably as much as 20 grains of the salicylate lying in the stomach, and there was a strong reaction in the urine after the fits had passed off, without any more of the drug being given."

I notice M. Ch. Féré records (*Progrès Médical*, December, 1888, p. 452), that there is a lowering of tension in the renal vessels at the end of the epileptic paroxysm, accompanied by increased elimination of drugs, and this demonstrates that there was high tension and diminished elimination of drugs during the paroxysm, and illustrates what I have said on the subject in reference to fig. 33.

I can explain the facts much more completely than at the time the above was written, for I know now that when uric acid in the blood raises arterial tension it obstructs the capillaries throughout the whole body. So that not only are the urine and saliva scanty, not only is the skin cold and dry, but all the gastro-intestinal secretions (gastric juice, bile, pancreatic and intestinal juices), are similarly diminished, and the circulation through their mucous membranes is so imperfect that digestion and absorption come to a standstill. This and the generally diminished metabolism accounts for the marked fall in urea excretion that generally accompanies a plus excretion of uric acid, and the resumption of these physiological processes accounts for the rise of urea when the urates are cleared out of the blood, and their excretion in the urine diminished.

Such a marked arrest of gastro-intestinal digestion will almost certainly be accompanied by the onset of putrefactive processes, of which Herter and Smith have observed some results.

All is now clear; the reason the salicylate failed to appear in the urine in the above case was because the capillaries were obstructed, and gastro-intestinal digestion and absorption were at a standstill.

The origin of the horribly fœtid dejecta often met with after an attack of dyspepsia, bilious attack, or uric acid storm, is clear, also why calomel is so valuable. I believed that it acted as an antiseptic, but it is now evident that its most important action is the result of its chemical relation to uric acid, by which it clears urates out of the blood, frees the capillaries and allows gastro-intestinal digestion to proceed (see p. 66).

The intestinal putrefaction noticed by Herter and Smith, far from being the cause of the fits, is a result of collæmia. The obstruction of capillaries which produces the high blood pressure (in turn interfering with the intracranial circulation and producing fits), interferes also with gastro-intestinal digestion and allows putrefaction to take its place (see also the causation of oxaluria in chapter xii.).

Agostini (*Riv. di Pat. Nerve. Ment.*, iii., 1896), finds that the gastric juice after an attack of major epilepsy is toxic, causing when injected into rabbits, fall of temperature, slowness of respiration, weakness and general convulsions, and suggests that the stomach excretes some toxin which is circulating in the blood. I think the symptoms are not unlike those of uric acid collæmia in man, and also resemble those produced in rabbits by feeding with hypoxanthin (see chapter xvii.).

Like the headache, uric acid epilepsy is often periodical. M. H., the case whose excretion in a series of fits is given in the *Neurologisches Centralblatt*, has been under my care for a long time, and in her case the fits appear with considerable regularity every fourth week; occasionally there is a slighter attack at a two-week interval. Again, the fits almost always appear when the excretion of uric acid is naturally large—as in the early morning, when the acid tide of the night has run itself out, and with falling acidity there is a plus excretion of uric acid. On occasions too numerous to mention, the fits have been obviously precipitated by causes which would produce a uric acid fluctuation and its temporary excess in the blood.

One morning in the early alkaline tide a fit caused a bad fall which cut open her chin. Chloroform was administered, and the

wound sewn up, but the chloroform produced vomiting, and she had a series of extremely severe fits. Obviously the vomiting would diminish acidity and flood the blood with uric acid.

She has told me that though she has no warning of the individual fits, she generally feels more heavy and drowsy on waking on those mornings, and this is a parallel of the uric acid headache, the drowsiness and disinclination for getting out of bed being in both cases the work of uric acid, and a proof of its excess in the blood. Of the heaviness and stupor following the fits I have (*Brain*, Spring Number, 1891, p. 83) elsewhere pointed out that this also corresponds with the work of uric acid, but is not proportional to the severity of the fits.

I will mention a few points in treatment which this case appears to illustrate.

One of the first things I did after getting a uric acid reaction was to give salicylate of soda, and for a long time she did well, and said that she was brighter and better in herself—a remark made by many epileptics when put on this drug.

The fits, however, returned, and it is doubtful whether the apparent improvement was more than one of the natural fluctuations in the frequency of the attacks, as this drug was fully tried by Dr. Tooth at the National Hospital, Queen Square, and though most cases improved at first, they afterwards relapsed.

Salicylate of soda is a double-edged weapon; it promotes the excretion of uric acid, but in a disease like epilepsy this is often a cause of danger, for if it is taken irregularly its action may fail and leave a considerable amount of uric acid in the blood, and if some of this combines with an alkali it will produce a fit; a headache can be produced in the same way (see fig. 41). Again, salicylate will sometimes upset the stomach when taken irregularly or at the wrong hours, and this not only hinders the action of the drug, but causes a rise in alkalinity, and possibly a uric acid storm.

I believe that in epilepsy, even more than in headache, diet is the only hope of controlling uric acid. In the following case it appears that diet coupled with somewhat severe purgation stopped the fits, and I have mentioned (p. 213) a similar case from the experience of the late Dr. King Chambers. I have heard from a number of colleagues and others that they have followed my suggestions with more or less benefit to epileptic patients, though much more experience is required before we can take the results obtained as more than encouragement for experiment in similar cases.

This case is that of a gentlemen, aged 50, who had suffered from

fits all his life, and was cured by a severely vegetarian diet, with a purgative dose of calomel and colocynth, followed by Haust. Sennæ co. twice a week; he lived twenty years more without any fits.

He lost weight very decidedly, and was considerably weakened. I think it probable that the urate formation and introduction were not only greatly reduced, but that the heart was much weakened by the severe treatment, and hence was incapable of keeping up so much blood pressure as was necessary to compress the intracranial veins.

Probably this treatment was unnecessarily severe: at the same time there are numbers of epileptics who would be glad to purchase freedom at even greater cost.

The treatment in the above case was recommended by Dr. Pelham Warren, long since dead, and the directions say, "The medicine is meant to remedy the mischief arising from an inactive state of the liver, indigestion, &c., but the constitution cannot be freed from the unhappy tendency to pressure on the brain and convulsions without the strictest persevering attention to diet."

"Pressure on the brain" is a good and possibly accurate description of the condition, and reminds us of what patients with headache so often say—that their head is bursting.

Strychnine, which tends to raise the blood pressure by strengthening the muscles of the heart and vascular system, is generally considered to do harm in epilepsy, while the favourable action of antipyrin and bromide of ammonium, both of which lower the blood pressure, I have already discussed in connection with the uric acid headache.

Dr. W. A. Turner says in the *Lancet*, 1905, vol. i., p. 711: "Of the several forms of diet recommended in epilepsy I have found that of salt starvation or dechloridation most satisfactory," and this is interesting, for the same holds with regard to migraine. The effect of chloride of sodium being to raise the acidity of the urine and to diminish the alkalinity of the blood, it thus tends to cause fluctuations in the excretion of uric acid, and these are the cause in not a few cases either of headache or epilepsy. Disusing salt should therefore be useful. It acts in the same way as a steady application of alkali, and this is an advantageous treatment, permitting reduction of the amount of bromide which would be given.

I frequently observe that diet which is correctly chosen enables one to dispense with bromide in epilepsy and headache. It is often an advantage to take a certain amount of alkali daily to ensure the free passage of uric acid out of the body.

Dr. Turner states that the diet giving the most satisfactory results is one which (except for the use of eggs) is identical with

that which I advise, and I believe that were he to omit the eggs he would secure greater success.

I have heard from Dr. Logan, of Ecclefechan, N.B., that a case of epilepsy of twenty years' standing has apparently benefited very greatly by the diet treatment I suggested after bromide had failed; and a number of cases similarly improved on a diet of vegetables and milk are quoted by Dr. Ferguson, of Toronto, in a paper, "Some Remarks on Epilepsy," read before the Huron Medical Association, and in a later paper (*Alienist and Neurologist*, April, 1893). Dr. J. T. Eskridge, of Denver, Colorado, has written on these subjects in the *Alienist and Neurologist* for January, 1892, and I have since heard that he is getting many excellent results.

Sir W. H. Broadbent, in his book on "The Pulse," p. 120, says, in reference to Tripiers's theories about the pulse of epilepsy: "I think it is the slowing of the circulation which causes the convulsions," and a little further on, "I look upon convulsive attacks, when they occur in connection with an infrequent pulse, as a result of cerebral anæmia, produced exactly in the same way as the convulsions after great hæmorrhage"; and again, "The late Dr. Moxon, it will be remembered, went so far as to suggest that the initial event in common epilepsy was a stoppage of the heart." See also an interesting paper, "Experimentale Untersuchungen über Anæmie und Hyperæmie des Gehirns in ihrer Beziehung zur Epilepsie" (*Archiv. de Physiologie*, June, 1891, p. 609).

It is interesting to note that Dr. S. West has pointed out (*Lancet*, 1896, vol. i., p. 1478) that digitalis and belladonna are valuable additions to bromides in epilepsy, for if digitalis strengthens the heart it may prevent it stopping as the result of temporary failure before high blood pressure (see also cases to be mentioned where hæmorrhage stopped with the onset of a fit).

I believe we have in the effects of uric acid on the circulation —about which I have said so much—a direct cause of just such alterations in the cerebral circulation as Sir W. H. Broadbent mentions. I should be inclined to state the case for the causation of fits by uric acid as follows: In 1888 I pointed out that some epileptic fits are accompanied by a characteristic fluctuation in the excretion of uric acid, in that there is a minus excretion before and after the fits, and a corresponding plus excretion during continuance, an observation since repeated by myself and others, while very many of the signs and symptoms of epileptic and other fits are the signs of collæmia.

Further, it is very improbable that the fits are the cause of the

large excretion of uric acid, because this is the natural result of a fluctuation in excretion hours before the fits began. It is extremely probable that uric acid is the cause of the fits, because I can practically prove that it may produce such changes in the circulation (stasis, &c.) as Sir W. H. Broadbent and others believe to be the cause of them (see pp. 259-261, and *Brain*, Spring and Summer Numbers, 1893). The same argument applies to the causation of puerperal and uræmic convulsions. Pregnancy is a time of greatly increased metabolism, during which there will be considerable storage of uric acid which finds its way into the blood as soon as digestion and metabolism are upset by the pains and fatigues of delivery. In Bright's disease again there is nearly always high blood pressure and excess of uric acid in the blood, and it needs but a slight fluctuation in excretion to produce stasis and hyperæmia in the intracranial circulation, and possibly œdema of membranes as well.

There is a note in the *Epitome of the Brit. Med. Journ.*, 1903, vol. i., p. 101, on high blood pressure in the amaurosis of lead colic, uræmia and eclampsia.

With regard to lead colic it is pointed out that amaurosis only occurs during the attack, and disappears with it, and is probably due to the high blood pressure.

The changes which produce transitory amaurosis are probably situated in the occipital lobes and consist of the contraction of the vessels. The author's contention is that the one condition common to the temporary disturbances of vision occurring in lead colic, uræmia and eclampsia is high blood pressure, and this creates difficulties in the explanation of the above-mentioned contraction, for he proceeds to say that the cause of this contraction and consequent cerebral anæmia is uncertain, since an experimental rise in general blood pressure is followed by cerebral hyperæmia. This is from my point of view a valuable record, for I have long maintained that uræmia is nothing but high blood pressure and its resulting œdema of the brain produced in the manner described in the previous chapter, and acknowledging that uric acid is the cause of this high blood pressure we can immediately explain the phenomena.

The relation of lead colic is the relation of a great excess of uric acid in the blood, which it produces in the same way that other forms of severe dyspepsia do in relation to uræmia and eclampsia. The relation of the causation of this œdema to the high blood pressure is defective intracranial circulation produced by uric acid; and amaurosis occurs during the attack of colic and disappears with

it, for the same reason that temporary glycosuria appears in relation to lead colic (see chapter xiv.). Amaurosis also occurs occasionally in a case of migraine, and is then no doubt the result of the circulation changes. We can thus explain what the writer quoted is unable to understand. The amaurosis was due to cerebral anæmia produced in the manner described in speaking of migraine. It was the result of high blood pressure and obstruction of the capillaries by uric acid, but when the author of the paper produced general high blood pressure he did not act, as uric acid does, by obstructing all the capillaries throughout the body (which he was probably unable to do), but by increasing the fluid in the vascular system or augmenting the driving power of the heart, and this would, in the absence of blocking of the cerebral capillaries and of the slowly produced cerebral œdema, cause hyperæmia of the brain and not anæmia.

The value of a non-meat diet in pregnancy has been discovered empirically by others, and it would appear from what they say that many of the troubles of pregnancy and child-birth are the results of dietetic errors (see *Brit. Med. Journ.*, 1895, vol. ii., p. 99, also further on as to the causation of fatigue, and for cases see p. 627).

I know experimentally and from others that similar diet has greatly relieved menstrual troubles, such as dysmenorrhœa and menorrhagia; I think that it probably acts in both conditions by lowering blood pressure and relieving the heart, and thus preventing congestion of the hepatic, abdominal, and pelvic circulations, about which I shall speak in chapter xiv.

Dysmenorrhœa, menorrhagia and other congestive pelvic troubles are very often associated with slow capillary reflux and high blood pressure, and these cases I have often relieved by controlling blood pressure.

Many of these cases are unfortunately treated as due to weakness and debility, in spite of an obviously hypertrophied heart and blood pressure far above normal: they are given considerable quantities of meat, wine, and meat extracts, and serious results occasionally follow.

There are in many such cases (with our present knowledge) the plainest indications that the circulation is the only thing which is at fault and requires treatment.

I believe that hysteria and hysterical fits bear the same relation to uric acid as epilepsy, and that many of the minor symptoms of hysteria are signs of collæmia.

I have said (chapter iv.) that the passage of a large quantity of

uric acid through the blood is generally accompanied by a fall in the excretion of urea (*i.e.*, probably in the formation of urea), while, on the other hand, the clearing of uric acid out of the blood by anything that quickly produces this effect is followed by a rise of urea. These fluctuations afford a partial measure of the effects of uric acid on metabolism, and have suggested to me that the rise of urea noticed by MM. Gilles de la Tourette and Cathlineau (*Progrès Médical*, 1889, vol. i.) as occurring at the end of an attack of hysteria is due to the same causes. They observe that urea is diminished in the twenty-four hours including the attack, and, when the attack is coming to an end as the capillaries begin to get free, there is a rise of urea from increased metabolism; doubtless the circulatory troubles which interfere with metabolism in the muscles, liver, &c., will delay or temporarily suspend gastric digestion also. They mention that there is a marked temporary polyuria affecting the first micturition after the attack, and that the cause of this is not completely known; but if the attack is attended, as I believe, by high blood pressure and obstructed capillaries, and if (as it passes off) the capillaries are freed, there is not much difficulty in completely explaining the temporary diuresis (see p. 22). Probably the best statement would be that the freeing of capillaries which ensures a good circulation in the kidney and a diuresis, ensures also a satisfactory circulation in the brain, and the mental faculties regain their normal equilibrium. It is the circulation which acts on the nerve centres as it acts on the skin, muscles, liver and kidneys, and perturbs their functions.

I have found excess of uric acid in the urine in some hysterical attacks, and I consider the nervous symptoms as the results of the circulatory disturbances produced by collæmia. This cause will account for the fall of urea during, and the rise after, as well as for the diuresis following the attack which these authors are unable to explain.

This view that hysteria, neurasthenia and functional neuroses are results of a morbid condition of the blood is upheld by Biernacki in an article in *Neurolog. Centralb.*, March, 1898.

He considers that the blood changes are due to disturbance of oxidation processes, and that this explains the frequent connection of hysteria with the uric acid diathesis, an observation confirming my own contribution of facts.

But the uric acid diathesis is a myth, and deficient oxidation as a cause of it is another, the excess of uric acid in the blood and urine being due to nothing except excessive introduction and defective elimination, while such defective metabolism as occurs is the result of the influence of uric acid on the circulation.

The above observer would say:—

(1) Defective oxidation.

(2) Blood changes and excess of uric acid.

(3) Functional neuroses.

While I can demonstrate that the chain of causation is:—

(1) Excessive introduction and defective elimination of uric acid.

(2) Collæmia.

(3) Defective circulation.

(4) Functional neuroses accompanied by defective metabolism, with falling urea as its sign.

The control of uric acid controls the circulation, and the functional neuroses and metabolic phenomena (including chlorosis and anæmia) are secondary.

This gives us power over the circulation of the blood and its quality, little, if anything, short of absolute.

However high the blood pressure, I can bring it to normal in from six to twelve months by diet, or in about as many days by drugs, provided there is no organic disease (see cases in chapter xiii.), and the normal blood pressure will be maintained so long as there is effective control of uric acid.

With the altered blood pressure and improved blood and metabolism the neuroses get less marked, and may disappear completely.

Epilepsy is not only, as has long been known, related to gout and to migraine, but has an important relation to the relative excretion of uric acid in the urine; an excess of uric acid in the urine being the index of an excess in the blood, and this by its effects on the vessels, may be the actual cause of such changes in the cerebral circulation as occasion fits.

These observations and reasoning, founded on clinical relationship, appear to afford a fairly good working explanation of the causation of these diseases.

I still ask, "Is the Uric Acid fluctuation a cause or a consequence of the Epileptic Fit?" And from whatever point I look at it; whether I regard the relation of the excretion to the fit, and the fact that the plus excretion is the result of a minus excretion preceding the fit, and therefore not caused by it; or whether I regard the important series of parallels between an epileptic fit and a uric acid headache; or when I look at the powerful effects of uric acid on the circulation, nutrition and function of many important organs and tissues, I seem to get only one answer, "cause."

If uric acid causes the fits we should be able to control them

in something the same way as the uric acid headache (migraine), for I may claim that I have absolutely controlled the headache attacks, with the capillary circulation and blood pressure, by clearing and keeping the blood clear of uric acid.

Can the same be done for epilepsy? It will certainly be more difficult, but should not be impossible, though the absolute amount of control may be less than with the headaches.

In headache there is a large and comparatively slow fluctuation in the excretion of uric acid, *i.e.*, a man has a headache to-day because yesterday in the alkaline tide something interfered with his urate excretion and he passed out only half the quantity usual in the same hours; the uric acid held back yesterday is added to the natural excretion to-day, and there is enough in his blood for a few hours to affect blood pressure and intracranial circulation.

The object attained by diet is so to reduce the intake and formation of uric acid that the largest quantity resulting from such a fluctuation shall never, or rarely, be sufficient to affect the blood pressure and the intracranial circulation to a serious extent.

In epilepsy (as will appear from my clinical results) the fluctuation is shorter and steeper, for two to three hours there is a very powerful retention of uric acid during which the patient feels unusually well, and this is followed in the next two hours by an equally short and sharp plus excretion of all the uric acid retained.

In a word, the epileptic wave of excretion runs very high but only for a short time, and it is difficult to keep the general level of uric acid excretion so low that these waves shall not occasionally get high enough to do damage by raising the blood pressure and affecting the intracranial circulation.

I note that Sir W. Gowers remarks (*Lancet*, 1895, vol. i., p. 1626) that the visual sensations of epilepsy last seconds, those of migraine minutes, while the convulsion of epilepsy lasts minutes, and the paroxysm of migraine hours.

The parallels between the uric acid headache and the epileptic fits are so instructive that I present them in tabular form.

(1) They have no morbid anatomy.*

(2) Are periodical.

(3) Occur for years or for life.

Migraine and epilepsy of puberty resemble chlorosis, and may cease as the collæmia (post-developmental) passes off.

(4) Occur together or alternately.

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* Wynne, *Lancet*, 1893, vol. ii., p. 434.

(5) Preceded by minus uric acid excretion, accompanied as usual by feelings of well-being.

(6) Accompanied by plus uric acid excretion, and bear a generally similar relation to diurnal variations in uric acid excretion.

(7) Worse at or about menstrual period.

(8) Better during pregnancy and worse after delivery.*

(9) Better during fevers and worse after them.†

Dr. J. R. Charles, in the *British Medical Journal*, 1900, vol. i., p. 767, says, speaking of enteric fever: "When such a patient is well advanced in convalescence one is surprised to find he suffers from fits, and on enquiry one learns that he was previously epileptic; in other words, the fits have been in abeyance during the febrile and post-febrile stages. I have never seen a fit during the febrile period." He quotes from others to the effect that several other diseases, as measles, erysipelas, and acute pneumonia diminish the frequency of epileptic seizures; and if epilepsy is due to excess of uric acid in the blood, and the circulation changes thus produced, there is little difficulty in explanation, for fever is a process which lowers the blood pressure, and at the end of a long and weakening fever it takes some time before blood pressure can rise, even though uric acid begins to be again freely present in the circulation, almost as soon as the temperature falls. In all these cases, as in migraine, the attacks are absent during acute fever, but return when the temperature becomes sub-normal, and are often more frequent and severe.

In 7, 8, and 9 both exhibit a remarkable parallel with another disease due to uric acid, viz., Raynaud's disease (see chapter xi.); also to a certain extent with chorea, which is sometimes associated as to its onset with post-febrile or menstrual collæmia. Workers at the relation between malaria and epilepsy have noted (*British Medical Journal*, 1900, vol. i., p. 337) "that generally the epileptic attacks appeared in the interval of the malaria," *i.e.*, in the period of post-febrile collæmia, just as do migraine and Raynaud's disease.

(10) Preceded by high blood pressure‡ and irregular pulse, with coldness and numbness of the extremities, and shivering.

(11) Bear similar relations to gout, rheumatism, and other uric acid diseases.

(12) Preceded or accompanied by subnormal temperature.

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* Oliver, *Lancet*, 1894, vol. i., p. 1295; see also *British Medical Journal*, 1891, vol. ii., pp. 1120 and 1236.

† *Lancet*, 1894, vol. ii., p. 1438, and *British Medical Journal*, 1898, vol. i., p. 1125.

‡ Féré, *Progrès Médical*, 1889, vol. i., pp. 415 and 434, and vol. ii., p. 26.

(13) Followed by a fall of blood pressure and a diuresis.*

(14) Similarly related to dyspepsia and gastro-intestinal disturbance however caused.

(15) Similarly affected by weather and changes of temperature.

(16) Accompanied by more or less complete suspension of gastro-intestinal digestion and absorption.

(17) Accompanied or followed by albuminuria.†

(18) Preceded by marked changes in, or even complete loss of sight,‡ or by spectra, flashes of light, or other optical or sensory illusions, or by mental delusions.

(19) Similarly related to peripheral neuritis.§

(20) Precipitated or made worse by cold.

(21) Made worse by administration of quinine, iron,‖ or lead.

(22) Improved by nitrites, acids, or antipyrin.¶

(23) Relieved by compression of the carotid arteries.

(24) More or less completely cured by diet.

With regard to (6), it is remarkable how these two diseases tend to attack in the early morning hours. As the acid tide of the night is ending, and uric acid, for many hours below urea, tends to rise above it, as low blood pressure, free capillaries and quick pulse give place to the reversed conditions of early morning, and the reaction of the blood and urine passes from less to more alkaline till the point of greatest urate precipitation is reached. We have then also the greatest incidence of these, and allied diseases, *e.g.*, mental depression, asthma, angina. These facts have been verified by many observers, but the explanation was wanting.

In the headache a fluctuation in excretion of uric acid occurs in these early morning hours resembling that of the epileptic fit. It is comprehensible that a pathologically increased fluctuation should suffice to produce any of the effects mentioned.

Drs. Gossage and Coutts say, in a Discussion on Convulsions in Infancy (*British Medical Journal*, 1899, vol. ii., p. 462): "Asphyxia is one of the most powerful exciting causes of convulsions of all ages." After what I have said in chapter iii., p. 89, it will, I hope, be clear that asphyxia, by causing deficient oxidation and increased alkalinity of the blood induces that collæmic condition which I

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* Féré, *Progrès Médical*, 1881, vol. ii., p. 452.

† *Archiv. de Neurol.*, May, 1892, and *Journal of Mental Science*, April, 1899.

‡ Gowers, *Lancet*, 1895, vol. i., p. 1626.

§ Charcot, *Progrès Médical*, 1890, vol. ii., p. 83, and Cagney, *Lancet*, 1891, vol. ii., p. 1095.

‖ Radcliffe, *Practitioner*, 1883, vol. xxx., p. 95.

¶ *Lancet*, 1887, vol. ii., p. 1163.

believe to be the cause of all convulsions; asphyxia thus slowing the capillary reflux, raising blood pressure, and causing wide divergence between surface and deep temperatures.

In a paper by Dr. R. O. Moon, *Lancet*, 1904, vol. ii., p. 1781, there is a quotation from Holt to the effect that in a nervous child a convulsion often means no more than an attack of migraine in an older person. I believe an epileptic convulsion generally means no more than this. It is probably an exaggeration of the condition producing a migraine headache acting perhaps on a person whose intracranial circulation is for certain anatomical or physiological reasons specially liable to be upset by changes in the blood pressure, and this is practically always the case in children, as compared with adults. As the child grows up he may suffer from migraine, and no longer from epilepsy or convulsions. It is by no means uncommon to find both conditions in one family, and often to find them alternating in one individual.

Dr. Moon's conclusion seems to be that all convulsions that occur in infancy are of serious import, and point to the need of careful supervision for children who suffer from even a single fit in childhood; a conclusion with which I entirely agree.

There is here another parallel between convulsions and the uric acid headache, for this is increased or precipitated by bad air in crowded rooms.

The asphyxia is not the cause of the uric acid in either case, for in its absence there is no headache; given sufficient uric acid, asphyxia causes collæmia, with the usual results.

It follows that if the blood passes to the alkaline side of the collæmic point in the later morning hours (say 8.0 a.m. and 9.0 a.m., fig. 3), it must pass back through the collæmic point as the acidity rises about 11.0 a.m. or 12.0 noon. This explains the beginning or return of headache about these hours.

The effect of the collæmia depends partly on the amount of uric acid, and partly upon whether the reaction of the blood tends to linger about the collæmic point, or to pass quickly to one side or the other; this also explains the effects of a few grains of bicarbonate of soda, comparatively little in some cases being needed to turn the scale to the alkaline side.

There is the closest parallel between the uric acid headache and the fits of epilepsy, or uræmic, puerperal and other convulsions.

If all are due to uric acid, nothing is more simple than the causation of this extensive parallelism; it is otherwise inexplicable.

A series of papers by Drs. J. Voisin and R. Petit on epilepsy as

due to intoxication, appeared in the *Archives de Neurologie*, 1895, Nos. 98, 99, 100, *et seq.*, and I have referred to a paper by Dr. Wynne, who argues in favour of similar causation. Drs. Voisin and Petit do not appear to have seen my previous writings, nor have they as yet identified any poison; yet their argument strongly supports my own, and I can show that almost everyone of their points can be explained if it be granted that uric acid is the toxic substance. Observers of my results in these and other directions will, I hope, have no difficulty in admitting that it is toxic.

I mention one or two points in their papers bearing on uric acid as the cause of epilepsy.

They lay great stress on the occurrence of gastric troubles before and during the fits or series of fits, but if the series is ending, the tongue clears, and the gastric symptoms subside; if they do not subside, the epileptic phenomena continue.

The explanation is simple when we know that every gastric upset brings excess of uric acid into the blood. It is thus the cause of the collæmia which causes the fits, malaise, headache, and all other symptoms, and in its turn intensifies the gastric upset, and adds putrefaction with possible formation of other toxic products.

But the gastric troubles themselves are the result of intoxication by uric acid, for in migraine, if the blood is clear of uric acid, both the gastric troubles and the headache paroxysm are absent.

With regard to the urine, they point out that there is diminished toxicity before and during, and increased toxicity after the fit, and it is interecting to note the parallel between the excretion of uric acid (which the authors have not estimated, though they notice in one case a deposit after a fit) and the toxic substance.

As regards its diminution during the fit we know that uric acid as shown by the blood granules may be in excess in the blood for thirty to sixty minutes before a corresponding excess appears in the urine (see fig. 21).

The authors mention an extremely interesting case when a wound that was being dressed stopped bleeding with the onset of a fit, and no pulse could be felt at the wrist. At the end of the spasmodic stage the pulse reappeared, beating 142, blood pressure rose, and the wound bled freely once more.

Here the fit was probably due to stoppage of the heart, which failed before the high blood pressure; with the fall of blood pressure (due to the stoppage of the heart) circulation practically ceased, the wound stopped bleeding, and the corresponding stasis in the cerebral circuit produced the convulsion. Later, the pres-

sure having fallen, the heart recovered and began beating again, and the pressure rose above normal after the fit, though probably not so high as it was just before when the heart failed. I have seen many cases in which the heart gave obvious signs of impending failure under the high blood pressure produced by uric acid, in the uric acid headache (migraine). These differ from this case of epilepsy merely in the fact that the heart, though threatening to fail, did not fail, and therefore no convulsion supervened. And these severe paroxysms of headache may, like the epileptic fit, be followed by albuminuria.

I am reminded here of paroxysmal albuminuria, hæmoglobinuria (which I believe this albuminuria resembles, see chapters xii. and xiii.), and so of the blood changes taking place in paroxysmal hæmoglobinuria and anæmia from the presence of excess of uric acid in the blood stream. I have therefore been interested by the authors' statement that a diminution of hæmoglobin and an increase of hæmatoblasts have been observed in connection with the fits. This is a change which I considered probable in epilepsy, because my own blood varies its quality hourly and daily in accordance with the amount of uric acid present. In the case to be presently related, Dr. Huntley kindly examined the blood after one or two fits, but with indefinite results. I hope for a personal examination in some future cases, as I have yet to learn at what length of time after the fit the blood changes are most apparent; probably after or during albuminuria, when present.

The authors also point out that repair of wounds is defective whilst epileptic phenomena continue, and only proceeds after the toxin has been eliminated. This is the work of uric acid, for I have stated that opium (which surgeons use to aid the repair of skin wounds) acts by clearing the blood of uric acid, thus allowing a free capillary circulation in the skin, which is impossible so long as the blood is full of uric acid.

Many troubles of mind and its adjustment mentioned by the authors are so obviously similar in migraine and epilepsy, and so obviously due to uric acid, as to need no comment.

The authors point out that epileptics come of a degenerate stock and one subject to kindred troubles and defects; one must not forget the fact that several men whose names stand large on the pages of the past, suffered from epilepsy,* or that migraine is common among those who work with their brains.

Migraine is intensely hereditary, but the inheritance is probably,

* Sir J. Crichton-Browne, *Lancet*, 1895, vol. ii., p. 74.

as I have shown (*Brain*, Spring and Summer Number, 1893, p. 250), merely anatomical, viz., the size of the arteries supplying the brain.

But in migraine, if you control the uric acid, you may entirely neglect the anatomical inheritance, which is then an advantage rather than otherwise.

Epilepsy may also be in part the result of large arteries, and therefore may coincide with considerable mental power, while the eventual crippling of mind referred to by Sir J. Crichton-Browne (prev. ref.) may be a result of repeated congestion, strain and œdema, with stasis and thrombosis, produced by recurrent collæmia and high blood pressure.

The above-mentioned author observed that in "dreamy mental states," which he considers allied to epilepsy, a diet rich in animal food did harm, and also quotes cases of epilepsy as similarly affected by diet.

Three generations at least in my own family have been affected with migraine, but in the second and third diet has completely controlled it.

I agree with the authors that an accumulating poison gives the best explanation of the attacks, and I have for many years indicated uric acid as the probable poison.

The authors dwell on the liability of women to epilepsy at the menstrual period and the regularity with which attacks then recur, and their observation confirms my own (see figs. 31 and 32).

If the facts I have collected regarding the relationship between the fits and excretion of uric acid stood alone, they would be worthy of careful consideration, but linked by a close similarity to migraine, and the further fact of control and prevention by control of uric acid they amount to a demonstration of causation.

The authors divide epilepsy into (1) Reflex, and (2) Toxic; the latter is further sub-divided into (*a*) that due to auto-intoxication; (*β*) that due to hetero-intoxication.

Obviously uric acid may account for toxic epilepsy by auto-intoxication, but even here my researches show that much of the required uric acid was exogenous and introduced with food. Having all these points in mind, I decided to investigate the following case, controlling the uric acid as carefully as possible and observing any response of the fits.

Emma S., aged 20, admitted into the Royal Hospital for Children and Women, on December 7, 1894.*

* This case and some of the above arguments will be found in *Brain*, part lxxiii., 1896.

Fits began when she was fourteen, and occur weekly, often on the same day each week. Menstruation began at the age of fifteen, and was regular, but did not occur during her stay in hospital. Her father and mother are well, but the latter suffers from headache. Eleven healthy brothers and sisters.

I examined the urine excreted before, during and after many fits, and got uric acid fluctuations identical with those of other cases, or in that first published (prev. ref.).

She was kept in bed to avoid fluctuations from muscular exertion or changes of temperature, and diet and drugs were altered according to a pre-arranged plan for controlling the introduction, formation and excretion of uric acid.

I give the excretions of only one or two fits, as most were practically identical, and in all there was a large excretion of uric acid in the hour following the fit, having a relation to urea of from 1—20 to 1—8.

During the daytime she passed water as far as possible hourly, so that when a fit occurred there would be little admixture of urine in the bladder.

If a fit occurred, say at 3 p.m., we had got the urine passed at 2 p.m., and this was called *before*. A catheter was passed at the time of the fit, and what it brought away was called *during*, and water was drawn or passed one hour after the fit, and that was called *after*.

After always contained an excessive amount of uric acid, both absolutely and relatively to urea.

Before generally contained a normal or subnormal quantity.

During sometimes contained a considerable excess, at other times only a slight excess, according as the separation corresponded more or less accurately with the changes of secretion. If urine were passed at 4 p.m., and if just as it were going to be passed at 5 p.m. a fit occurred, then the 5 p.m. urine might be called *during*, but would obviously be mixed with the excretion of say three-quarters of an hour preceding the fit in which the excretion was small.

But remembering these causes of fluctuation one always got a great excess of uric acid in the hour after the fit, and a more moderate excess in the urine drawn at the time.

Thus on the day of admission she had a fit.

Before, passed at 2.15 p.m., pale straw coloured, 1009, gave—

Acidity	... =	1·0 cc. of decinormal soda solution.	
Urea	... =	·75 per cent.	1—23 = 1 of uric acid to 23 of urea (nearly).
Uric acid	... =	·03360 ,,	

During, drawn off at the time of the fit, at 4.45 p.m., turbid, 1012, gave—

Acidity ... = 1·2 cc. decinormal soda.
Urea ... = 1·0 per cent. } = 1—17 (nearly).
Uric acid ... = ·06048 ,, }

Obviously, there was a mixture of *during*, with the urine of two and a half hours before the fit.

After.—Urine drawn at 5.45 p.m., one hour after the fit, was 60 cc., amber, turbid, 1020, and gave—

Acidity = 7·6 cc. decinormal soda = 4·4 grs. per hour of acidity, calculated as oxalic acid.
Urea ... = 1·1 per cent. = 10·1 grs. urea.
Uric acid = ·10080 ,, = ·92 ,, uric acid.
Relation uric acid to urea, 1—11.

February 27, 1895.—Urine of twenty-four hours, ending this morning, was 1275 cc., turbid, 1014, and gave—

Acidity ... 4·0 cc. = 49·2 grs. in twenty-four hours, = 2·0 grs. per hour.
Urea ... 1·8 per cent. = 351 grs. = 14·0 grs. per hour. } 1—37.
Uric acid ·04704 per cent. = 9·1 grs. = ·37 grs. per hour. }

On this day she had a fit, and the urine *during* was lost, the specimen *after* was saved, and was the excretion of exactly one hour.

It was 57 cc., amber, slightly turbid, 1022, and gave—

Acidity ... ... 8·4 cc. = 4·6 grs.
Urea ... ... 1·8 per cent. = 13·8 ,, } 1—13.
Uric acid ... ·13440 ,, = 1·03 ,, }

This shows, as compared with the hourly excretion of the day before the fit, that urea was slightly diminished after the fit, while uric acid was nearly three times as much after as before it.*

The urine after a fit therefore has generally these characters; it has a high sp. gr., often very high as compared with *before* and *during*. It is often turbid, and deposits urates, or uric acid, or both.

It is highly acid, this being, I think, partly due to the large amount of uric acid it contains. This rise of acidity, however

* Compare with the causation of fatigue in chapter viii.

comes only after the fit, and is no proof whatever that before and at the time the blood was not strongly alkaline, and therefore in a condition to hold much uric acid in solution.

Take another example, March 10, 1895.

Urine of 24 hours, slightly turbid, 1014.

Urea	1·6 per cent.	1—44.
Uric acid	·03696 per cent.	

Urine 4 hours before the fit 1010.

Urea	·9 per cent.	1—34.
Uric acid	·02688 per cent.	

Urine drawn at time of fit, containing of course also the excretion of the previous 4 hours.

Acidity	·88 cc.	
Urea	1·2 per cent.	1—40.
Uric acid ...	·0302 per cent.	

Urine one hour after the fit, pale amber, turbid, 1022.

Acidity	5·6 cc.	
Urea	1·0 per cent.	1—20.
Uric acid ...	·05040 per cent.	

Here we have diminished excretion 1—44 in the twenty-four hours preceding the fit, slightly increased excretion 1—34 in the urine passed four hours before the fit.

A diminished excretion in the urine drawn at the time of the fit, being also the excretion of the four precedent hours, 1—40, showing that there was a fluctuation in the direction of minus excretion in the hours immediately precedent.

And lastly, we have a plus excretion in the hour following the fit, this being, I think, probably composed of a very large excretion in the 20—30 minutes following the fit with a lessened excretion after this, the differences in the suddenness and steepness of the waves of fluctuation accounting for the difference in relation found after different fits.

With regard to the large excretion *after* the fit, we must bear in mind that it is the uric acid in the blood that alters the blood pressure and affects the intracranial circulation; and it is only after it has been in excess in the blood for some 30—40 minutes that it begins to be found in excess in the urine.

As regards effects on the blood pressure and intracranial circulation, these are probably most marked just at the time of change

from low to high pressure, hence the fit comes early in the collæmia and precedes the great excretion of uric acid.

See again March 19, 1895, urine of twenty-four hours, ending 8.0 a.m., 1—24.

Urine at 9.15 a.m., 1—56.

Urine at 12.15 p.m., time of fit 1—70.

Urine after fit, 1.15 p.m., 1—9.

Here we have a rather plus excretion on the day before the fit, a considerable retention before 9 a.m., a greater retention between 9 and 12, followed by a great plus excretion between 12 and 1 p.m.

Evidently the fluctuation producing this fit began about 7 or 8 a.m., and retention continued and increased up to about 12 noon; then followed the opposite and resulting plus excretion, producing the fit at 12.15 and the excretion of 1—9 between that and 1.15 p.m. (see Effects of Diet and Weather, figs 39 and 40).

The parallel between this fluctuation and that producing the uric acid headache is almost absolute; the differences are those of time and degree only.

The uric acid headache can be controlled by controlling uric acid to an extent which leaves little to be desired; can uric acid epilepsy be controlled by the same means?

This is the question I endeavoured to answer by observing this case, and I chose it in preference to others, because the history showed that the fits were remarkably regular in their weekly cycle.

I examined the urine *before*, *during*, and *after* more than fifteen fits, and the results were, as regards the main points, practically identical with those given. I would undertake to tell in any case when urine was collected in this manner, which was the urine of the hour following the fit. This urine also has a characteristic of very great importance, viz., that when a patient is taking drugs, such as an iodide or a salicylate, giving a marked reaction in the urine, such reaction is almost completely absent from the urine passed in the hour following the fit.

I, fortunately, noticed this point in the urine of the first case of epilepsy I examined, and I have mentioned it in reference to the observations of Herter and Smith on putrefaction in the intestines, and as explaining also the oxaluria of paroxysmal hæmoglobinuria (see chapter xii.) and dyspepsia, and the presence of excess of putrefactive products from the intestines in the urine after an epileptic fit. Not only is there no absorption of drugs from the stomach and intestines, but putrefaction takes the place of digestion, and the products formed under its influence account com-

pletely for the oxalates and excess of ethereal sulphates found later in the urine.

These authors suggest that these putrefactive products may represent the cause of the fit, but this is, in my opinion, to transpose causation. The only complete explanation is that the circulatory changes which excess of uric acid in the blood produces, affect the intracranial circulation and produce the fit, and also the stomach and intestines, and bring digestion and absorption to a standstill. Failure of absorption explains the absence of the drugs from the urine, and excess of putrefaction explains the production of the products ultimately appearing. The same thing occurs in the uric acid headache, for when this is severe, drugs introduced into the stomach produce absolutely no physiological effect, and do not appear in the urine till the headache is passing off; while if the gastric upset is continued it often ends in vomiting, and food is found to be almost undigested, though it has been in the stomach long enough to be completely digested and absorbed.

On December 30, 1894, Emma S. had a fit while taking salicylate of soda and iodide of potassium three times a day. The urine *before* the fit gave a quantity of iodide when a silver salt was added, and a dark purple with perchloride of iron.

Urine during gave distinctly less iodide.

Urine after, with a relation of uric acid to urea of 1—10, gave no iodide of silver, and only very slight purple with the iron.

I will now present the observations on this case in tabular form, noting also the interval between each fit and the one preceding, health, diet, drugs, and remarks. Any variations presented by the fits and the corresponding variations in diet and drugs made with the object of affecting uric acid will thus be clear.

First fit December 7, said to be one week after the previous one. Health and diet were ordinary, and she was taking no drugs.

December 10. Milk diet. Mixture containing perchloride of mercury and iodide of potassium.

December 19. Fit 12 days after previous one.

December 20. Mercury stopped. Iodide of potassium and salicylate of soda substituted. Milk diet.

December 30. Fit 11 days after preceding one.

January 2, 1895. Slight tonsillitis. Raised temperature, becoming normal on the 4th.

On January 6 she had a fit, 7 days after the previous one, but this short interval was probably in part the result of the tonsillitis, causing a fluctuation in urate excretion.

After the fit on January 6 the iodide was stopped and the salicylate given alone. All drugs were left off on January 12.

I now began to test the effects of diet.

No. of Fits	Date	Interval	Health	Diet	Drugs	Remarks
	1894	Days				
1	Dec. 7	7	Average	Ordinary	None	Soon after admission
1	,, 19	12	,,	Milk only	Iodide of mercury on Dec. 10	
1	,, 30	11	,,	,, ,, ...	Salicylate of soda 20th, and iodide of potassium	3 in 30
	1895					
1	Jan. 6	7	Tonsillitis Temp. normal on 4th	,, ,, ...	Salicylate of soda alone	
1	,, 18	12	Average	,, ,, ...	Salicylate of soda left off 12th	3 in 32
	,, 21	..	,,	Milk and fish ..	None	
	,, 24	..	,,	Milk, fish and meat	,, ...	
1	,, 31	13	,,	,, ,, ,,	,, ...	
1	Feb. 4	4	,,	,, ,, ,,	,, ...	
1	,, 11	7	,,	Milk, fish and meat, beef tea added	,, ...	3 in 17
1	,, 17	6	,,	16th. Beef tea off	,, ...	
	,, 21	..	.. ..	Meat off	,, ...	
	,, 25	..	.. ..	Fish off		
1	,, 27	10	Average	Milk only	,, ...	
1	Mar. 10	11	,,	,, ,, ...	,, ...	
	,, 11	..	,,	Milk and beef tea	,, ...	3 in 30
1	,, 19	9	,,	Milk only; last beef tea 16th	,, ...	
	,, 21	..	.. ..	Tea		
2	,, 25	6	Average	Farinaceous with 4 cups tea = 2-3 grs. th ein a day		
	,, 29	..	Temp. raised slightly	.. .. ..	.. .. ..	3 in 18
1	April 2	8	Average	Farinaceous and tea	None	
1	,, 6	4	,,	,, ,,	,, ...	
	,, 11	..	,,	,, no tea	,, ...	
1	,, 17	11	,,	,, ,,	,, ...	
1	,, 24	7	,,	,, ,,	,, ...	3 in 29
1	May 5	11	,,	,, ,,	,, ...	
	,, 6	..	,,	,, and tea again	,, ...	
1	,, 13	8	,,	.. .. ..	.. .. ..	
1	,, 21	8	,,	Farinaceous and tea again	None	3 in 26 *
1	,, 31	10	,,	Farinaceous and tea	,, ...	

* NOTE.—The previous 3 in 18 was probably partly the result of the beef tea.

On January 18 she had a fit, 12 days after the previous one, while she was still on milk.

On January 21 fish was added, and on 24th meat, and she con-

tinued to take milk, fish and meat till February 11, when beef tea was added. This lasted until February 16, when the beef tea was stopped, the meat following it on the 21st, and fish on the 25th. She was again on the milk diet.

She had a fit on January 31, 13 days after the previous one, making 3 fits in 32 days. At the date of the last fit she had been on fish for 10 days, and on meat for 7.

So far, then, diet had not affected the frequency of the fits, for 13 days was the longest interval; indeed, it seemed rather as if flesh food had increased the interval, which may easily be; for in the uric acid headache, taking meat every day does not produce a headache nearly so quickly as taking it only once or at one meal, the reason being that the daily introduction of uric acid tends at first to keep the blood clear, while a single dose does not raise acidity much, and when acidity falls uric acid gets into the blood and produces signs of its presence.

The next fit was on February 4, 4 days after the previous one, the next on February 11, and the next on February 17, 6 days later, making 3 fits in 17 days; a very different record from the two previous series.

From February 25 to March 11 she was on milk only; on March 11 beef tea was added and continued till March 16.

On February 27 she had a fit, 10 days after the previous one, a second on March 10, 11 days after it, being on milk only, and a third on March 19, 9 days later, when she had been on milk and beef tea for 8 days; this making 3 fits in 30 days, or the same record as the first two series.

Now came a surprise; on March 16 the beef tea was left off, and on March 21 she was put on farinaceous diet, which includes bread, puddings and tea in addition to milk.

She now had a fit on March 25 (or rather 2 close together which I count as 1, as both were due to the same fluctuation of urates), 6 days after the previous one; another on April 2, 8 days later, and a third on April 6, 4 days after that, making 3 fits in 18 days.

Though I had expected that the beef tea might have some effect, it was left off on March 16, and yet the shortest interval of all was that between the fit on April 6 and the one 4 days previous.

At this point I felt rather at sea; but I chanced to go into the ward just as she had finished her tea, and I saw that what remained was very dark coloured. This led me to enquire how much tea was included in the farinaceous diet, and I found that she had four breakfast cups a day. Further, enquiring as to the amount of tea

leaves used, and taking it that one pound of tea contains 175 grains of thein, I found that she was thus introducing nearly 3 grs. of thein a day.

We have seen that caffein, thein, theobromin and all similar xanthin compounds are practically equivalent to uric acid (see fig. 29), and she was thus taking the equivalent of at least 20 grs. of uric acid a week.

It was not surprising that with the help of the beef tea from March 11 to 16 her fits had been more frequent.

I stopped her tea on April 11, leaving her farinaceous diet otherwise as before.

She now had a fit on April 17, 11 days after the previous one, another on April 24, 7 days later, and a third on May 5, 11 days after that, making 3 fits in 29 days.

On May 6 she was again given tea, diet being otherwise unaltered, and she had a fit on May 13, 8 days after the previous one, a second on May 21, 8 days later, and a third on May 31, 10 days after that; making 3 fits in 26 days, or slightly quicker than in the previous series.

I now decided to try and diminish the frequency of fits, so I put her on farinaceous diet without tea, and gave salicylate of sodium with iodide of potassium, the former to eliminate as much as possible of the uric acid in her body, and the second to prevent it from combining with an alkali when in the blood, for it is apparently the combination of uric acid with alkaline or neutral phosphates in the blood which produces all the physiological and pathological effects I attribute to uric acid. I allowed her to get up, she having been in bed the whole of the previous period, about six months in all.

With this change of diet and drugs she went without a fit for a whole month, and had had no further attack when she left the hospital at the end of June.

The diet treatment did not cause any loss of weight as in the case previously mentioned, for she kept about 90—91 lbs. during the whole of her stay.

The fits according to history were very regular—one in a week, or 3 in 21 days. After admission, on milk only and some drugs, they fell to 3 in 30 and 3 in 32 days; animal food being put on, they quickened up to 3 in 17 days; this was stopped and they fell to 3 in 30 days; some beef tea and tea were given, and they quickened to 3 in 18 days; these were stopped, and they fell to 3 in 29 days, tea was resumed, and they quickened slightly to 3 in 26 days.

When tea was left off and some drugs were given, as at first,

they fell lower than during the whole of her previous stay in the hospital, 30 days elapsing without any fit.

Some may argue that this was chance and that there would have been the same variations without change in diet or drugs. Such an argument recommends itself little, for it passes the bounds of chance that the fits should have varied in such remarkable correspondence with the changes made in the uric acid introduction.

It discounts the numerous cases in which a diet free from or with reduced flesh food has produced a more or less marked alteration in the number of fits.*

It has been suggested that meat acts as a general stimulant to the nerve centres, like corn in the food of horses; but in the uric acid headache (migraine) this is certainly not the case, as it is not influenced by the general level of nitrogenous excretion, but only by the height of uric acid above urea, which is a measure of the quantity of uric acid passing through the blood. This headache can be produced by the ingestion of uric acid or equivalent xanthin compounds which increase the excretion of uric acid, but hardly affect total nitrogen; and in the above case it appears as if beef tea and tea, which introduced xanthin and uric acid, had a similar effect on the fits of epilepsy. In migraine you may keep urea well on the physiological level (3½ grs. per pound of body weight per day), and if this is done with milk and vegetable substances, which do not introduce much uric acid, there will be no increase of headache (see also fig. 73 and remarks on it).

The conclusive point about migraine is that if you control uric acid you control headache. I suggest that the same applies to epilepsy, only here the control must be more powerful, and may be more difficult to obtain.

This argument further ignores the fact that it is almost impossible to regard the uric acid fluctuation above described as a consequence of the fits since it begins hours before them; while it is easy to regard it as a cause, looking to the important influence which this substance exerts on the circulation, nutrition and function of all the tissues in the uric acid headache.

I believe that all gradations are to be met with from a mere temporary absence of mind to a severe epileptic fit. Nothing is more common than absence of mind in mental depression, or the uric acid headache (see also Sir J. Crichton-Browne, *Lancet*, 1895, vol. ii., p. 4, for many interesting connections between dreamy mental states, migraine and epilepsy).

* *Lancet*, 1895, vol i., p. 96.

I draw attention to an interesting paper by Dr. G. F. Still, on "Day Terrors in Children" (*Lancet*, 1900, vol. i., p. 292), where it appears these are found in children who are nervous and excitable, and come of rheumatic families and of families with weak-minded, epileptic or lunatic members.

Dr. Still remarks that the aura of epilepsy sometimes consists of a feeling of fear, and he classifies these terrors with the "paroxysmal neuroses," migraine and *petit mal*.

He considers that the dividing line between these terrors and some forms of insanity, epilepsy and hysteria is narrow; and it appears that there are all gradations between terrors and actual mania, so that the one may pass into the other.

These facts so strongly evidencing the close relationship of all these diseases and the gradation from the forgetfulness, selfishness and bad temper of mere high blood pressure, or migraine, through temporary absence of mind to *petit mal* and to a severe epileptic fit; and the similar gradation from momentary terrors and hysterical excitement to complete and lasting mania, are of the greatest possible interest, and form a stepping-stone from the causation of migraine and epilepsy to my remarks in the following chapter on the causation of mental disease.

I believe there underlies all these "paroxysmal neuroses" one cause—collæmia; hence their occurrence in rheumatic families, hence the observed alternation of migraine and the others with rheumatism; for when uric acid is deposited in the joints there is no collæmia.

The action of intestinal disturbance, which Dr. Still specially notices, is in all cases the same, and the dyspepsia of migraine disappears with the uric acid, as it is largely a co-result of the collæmia.

In the capillary reflux and the blood pressure we see one central factor of all "neuroses," and their measurement is frequently the clue to causation and treatment.

Results depend on such organic conditions as the form of the skull, the size of the arteries, their relations to the veins and sinuses, the presence of tumours or scars, and, more than all, on the strength and nutrition of the heart and its power to withstand collæmia and produce high blood pressure, with its results—headache, some forms of epilepsy and mental depression, to melancholia; or on its failure to overcome the collæmic obstruction causing temporary or permanent low blood pressure with its results, the conditions of excitement, hysteria or mania, and some forms of epilepsy; and cases of

melancholia have been recorded which alternated with gout just as headache does with gout or rheumatism.

"Neuroses" thus fall into two groups—the high blood pressure group associated with a strong heart, and the low blood pressure group associated with a weak heart, these latter being prominent in women with their weak muscle powers. Epilepsy is found in both groups, some cases being undoubtedly connected with sudden heart failure (and hence possibly the origin of epileptic mania) and others rather with the results of high blood pressure.

Now that we have almost absolute control over the circulation, the demonstration of these facts is easy; as in migraine, so in epilepsy and depression; so also in excitement, and hysteria, and in all minor and intermediate conditions, the cause being removed the effect follows.

In all cases diet will relieve or fail, and here we have a measure of the importance of the organic factor. Yet even when this is of great importance, diet begun early in life may prevent.

In a most interesting paper on "Hysterical Somnolence and States of Double Consciousness" (*Lancet*, 1900, vol. ii., p. 801), Dr. Ethel N. M. Williams says: "The question now naturally arises as to whether there is any pathological condition common to all these various states," and then dwells on the feeble tone of the vasomotor system and the similar but more marked phenomena in post-epileptic conditions. This is further evidence of the close relationship between all these circulatory disturbances, and the vasomotor system is unjustly blamed for the effects of the collæmia common to all.

My remarks upon the association of the uric acid headache with nephritis apply also to epilepsy in any case due to uric acid, for nephritis means chronic collæmia, and with this the fits will be more frequent and severe and less amenable to drugs and diet than in cases where the kidneys remain sound. Do we not get here a side light on the causation of the headache and fits of uræmia? As I have pointed out, the treatment of collæmia removes the symptoms of uræmia (*Brit. Med. Jour.*, November 30, 1889, and see also chapter xiii.).

To indicate the influence of uric acid in one family and the way epilepsy, migraine and other nerve troubles are connected I will mention one history: the father's father died of paralysis (probably cerebral hæmorrhage); the father extremely nervous; the mother intensely nervous, almost bordering on nervous mental excitement; one son epileptic; another son suffered from migraine; a third from

anæmia and neurasthenia—all this being obviously the result of one and the same cause acting through three generations. The signs and symptoms of uric acid in the circulation are well marked in all these cases, and those who were not anæmic to the point of disease had defective blood colour as compared with persons living on uric-acid-free diet.

Dr. C. Mordhorst, of Wiesbaden, has kindly given me notes of an interesting case. It was that of a lady whose knee and foot joints showed large deposits of urates, and who was ordered to take, in addition to hot baths, a strong alkaline water (Wiesbaden gout water). One day she took more of the water than had been ordered and at mid-day had a very severe attack of epilepsy, the first she had ever experienced. Dr. Mordhorst had her urine collected, and found it to give a relation of uric acid to urea of 1 to 15.

In another case he put a patient who suffered from epilepsy (1 to 2 attacks a week) on two bottles of Wiesbaden gout water a day, and while she took this quantity the attacks ceased, this coinciding with the observation of Dr. Tyson (see chapter vi.) on the effects of Vichy Water on Migraine.

She has now been on this treatment for three years, with the same good results. If the water is stopped, the attacks return.

This reminds one of the value attached to the use of alkalies as additions to the bromides in epilepsy by the late Dr. Radcliff (*Practitioner*, 1883, vol. xxx., p. 95). Dr. Radcliff used potash salts, and Dr. Mordhorst soda salts, but probably the effect was the same.

In the first case the alkali met with a large amount of urate, and brought into the blood on the day of the attack more than it could hold in solution, hence there was for a time considerable collæmia, resulting in high blood pressure sufficient to produce a fit.

In the other case where the alkali was taken steadily, the quantity of uric acid was probably never so large, and the alkali not only provided for a steady excretion of uric acid, thus preventing fluctuations (the great cause of attacks both of headache and epilepsy), but was able to hold the whole of the uric acid passing through the blood in fairly good solution (see remarks in chapter v.), so that collæmia was never severe. But as soon as the alkali was stopped, fluctuations in excretion again returned, and these presently sufficed to reproduce the fits.

It is by producing such fluctuations in urate excretion as are seen in fig. 13 that lead and other metals produce fits and are injurious in epilepsy; and apart from the action of any metals, similar fluctuations are evidenced by the feelings of well-being

often preceding a fit, so often in fact that patients themselves look on them as warnings. I also owe to Dr. Mordhorst the copy of a paper by Dr. Ackermann, "Zur Aetiologie der Epilepsie," from *Zeitsch. für die Behandlung Schwachsinniger und Epileptischer*, 1897, Nr. 2.

Reference is there made to Dr. Mordhorst's cases and to my writings on epilepsy, and it is suggested that the cause of this disease is direct irritation either of nerves or nerve centres by uric acid, thrown down by a local or general diminution of the alkalinity of the blood.

The natural outcome is the treatment of the disease by alkali in the form of Wiesbaden gout water, and several cases are related showing improvement, though some are, just as with diet, worse at first and better later. Doubtless in these cases there was at first too much uric acid for the alkali to hold in complete solution.

There are several points, however, in the above etiology with which I cannot agree, and it also fails to explain all the phenomena.

How, for instance, can any local irritation of nervous tissues account for the pain of headache or its relation to position and blood pressure? How can we explain the action of nitrites or the value of compression of the carotids in relieving headache or epilepsy, or again, the use of venesection in uræmia? It is true this latter may remove a small portion either of the acid or of uric acid, but its most obvious effect is surely that on blood pressure.

Again, acids are often useful both in epileptic fits and in the headache and drowsiness that precede or follow them, and the nitrites also diminish the alkalinity of the blood. I think the only possible explanation of all the phenomena is that the fits are due to high blood pressure with or without heart failure; that the high blood pressure is due to collæmia, which again depends on the quantity of uric acid available and its complete or incomplete solubility in the blood, which explains the observed effects of the alkalies used.

Among points of interest I notice Dr. Ackermann insists strongly on the absence of demonstrable changes in the anatomy of the nervous system, and the impossibility of reconciling any such changes with the irregular phenomena of the attacks.

He is inclined to think, however, that epilepsy cannot be explained without a disposition to formation of excess of uric acid (or the uric acid diathesis), and also supposes a special disposition of the nervous system in pregnant women during and after labour, and in children. All these points can, however, be explained by the influence of these physiological conditions on the formation, solubility,

and excretion of uric acid, and if there is any disposition of the nervous system, it has reference only to the size of the arteries supplying the brain.

He refers also to the difficulty in explaining the absence of uræmic phenomena in cases of anuria, but here again, though the blood may contain excess of urea, it will also probably contain plenty of acid salts. It will therefore be at least for some time a poor solvent of uric acid, and there will be no severe collæmia and high blood pressure, such as occurs in uræmia, till near the end; when with a general failure of nutrition and strength the blood becomes again perhaps a good solvent of uric acid, and more or less collæmia results.

He lays stress on the many points of resemblance between uræmia and epilepsy, and there are obviously more points of resemblance when we consider the headache, the eye symptoms, and the high blood pressure changes.

Dr. A. J. Hubbard, of Hemel Hempstead, makes the interesting suggestion that the convulsions of bottle-bed infants are partly due to the fact that in taking cow's milk, which contains one-third more casein than human milk, they are relatively on a highly nitrogenous diet and hence form some excess both of uric acid and urea. He has also found that salicylate of soda is of far more value in the treatment of these troubles than the alkalies commonly prescribed.

Diagnosis.—The time has not yet arrived for dogmatising; but where epileptic fits have recurred with more or less periodicity for a long time, and resemble migraine in their relation to dyspepsia, muscular exertion, or menstruation; where they are accompanied by scanty urine, and preceded by a slow and faltering pulse, with altered capillary circulation; when also there is no syphilis or other organic cause, I suggest that they may be due to the effects of uric acid on the circulation in the skull or on the action of the heart, and that further investigation or treatment from that point of view is indicated.

The Indications for Treatment are much the same as in migraine. An attempt may be made to break through the fits, or the attendant stupor and headache, by the use of such drugs as acids, calomel, morphine or the nitrites, with or without temporary compression of the carotid.*

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* For cases where this was done, see *Lancet*, 1892, vol. i., p. 358, and vol. ii., p. 662.

I have seen many cases where acids relieved the stupor and headache that follow the fits, and in some the patients would ask for their dose as they regained consciousness. It is interesting to remember that a drug which was at one time regarded as a specific for epilepsy, viz., nitrate of silver, acts in exactly the same way as the acids and other drugs mentioned above. If epilepsy is due to uric acid in the blood, it follows that it may be temporarily relieved by uric acid precipitants. And, if the precipitation is thorough, the tissues may act like a uric acid filter and keep the blood clear for some time. Thus in the *Therapeutic Gazette*, 1896, January 15, p. 30, some cases of epilepsy are reported as being cured by nitrate of silver, and it is remarked that argyria relieves many nervous troubles; but argyria means not only a deposit of silver, but a deposit of urate of silver, as I shall explain in the case of lead in chapter x., and the extensive deposit of urates in the fibrous tissues of the body means (just as in gout, see chapter xv.) that the blood is for a long time relatively clear of urates, hence there is no collæmia to cause epilepsy or other nervous troubles.

The diet treatment must often be very strict, and milk in small quantities the only animal food, or better still, perhaps, only the dry diet of bread stuffs and fruit advocated in chapter xvii. There must be no soup, meat extracts, strong tea or coffee, for it is useless to stop meat and admit substances of the same nature which are innutritious. When the heart is strong and the fits seem to be due to the effects of high blood pressure on the circulation of the brain, powerful purgation and a rather poor diet may not be bad treatment, but where the heart is weak and the fits seems to be due to its temporary failure before high blood pressure, every care should be taken to reduce uric acid without unduly reducing urea and nutrition, and it may be well perhaps to try for a time the use of some digitalis, which I mentioned as having been found useful by Dr. S. West. I find that many epileptics have very high blood pressure; thus, a patient I saw recently, who had had fits for years and was a great drinker of tea, had a blood pressure of 180 between the attacks. It may be as well to point out, with regard to diet treatment, that in this disease as in headache, mental depression and chlorosis (see fig. 60) the first effect of strict diet may be a temporary increase of collæmia and hence an increase in the frequency and severity of the fits. I mentioned this in an article on the treatment of these diseases in the Spring and Summer Number of *Brain*, 1897, and pointed out that it was necessary to guard against discouragement either of patient or doctor, as this

temporary increase is one more proof of its relationship to the excretion of uric acid and collæmia, and shows that the diet has only to be continued to produce relief or cure. I notice that many recent writers are stating, as the results of their experience, that long-continued milk diet frequently diminishes both the number and severity of the convulsions.

My own practical results continue to be very encouraging, and I hear from many others of good results with diet after bromides had failed.

I agree with Dr. E. J. Spratling (*Journal of Nervous and Mental Disease*, May, 1899), that recovery is only to be recorded in the case of patients who have for two consecutive years been free from epileptic attacks, and it takes time to get records of these. I think in many cases the result will be (as in migraine) rather a great reduction in the severity and number of the attacks, than complete recovery.

I have, however, got some marked results with diet alone as regards frequency and severity of attacks (the relatives often regarding the patients as cured, and wishing to relax the diet rules), and my results have been so good that I have not had to attempt the severe purging.

Among children I have records of several cases that have safely passed the above-mentioned time limit, and several of adults where the attacks have been nearly as markedly diminished as my own headaches; others again, though showing a decided diminution, still have frequent attacks. One of these had in 1899 62 attacks. Diet was begun in the middle of 1900, and there were in this year 54 attacks, in 1901 41 attacks, and so far in 1902 they are keeping about the same level as in 1901.

Not a few sufferers have become so saturated with the idea that epilepsy is an incurable disease, that they will only give the diet a half-hearted trial, and if it does not do the impossible, and still more if the attacks are more frequent at first, they give it up and yield to their craving for meat and other stimulants.

Nothing except a diet treatment of twelve to eighteen or twenty-four months is worth doing; though long before that, and even in or after the first few months, there should be a distinct improvement.

If this does not occur, if the blood pressure still remains high and the capillary circulation defective, more active measures, as the purging treatment, or the starvation treatment advised for migraine, may be tried; or these may be begun from the first in severe cases associated with very high blood pressure and very defective capillary circulation.

And in all cases the effects of treatment on the blood pressure and circulation must be considered.

In very acute conditions of puerperal and uræmic convulsions the blood pressure and capillary circulation must be observed in the same way and the treatment directed on the same lines.

Some very interesting cases of puerperal eclampsia treated by morphine and other retentives of uric acid, as liq. ammon. acet., are recorded by Mr. G. E. Fitzgerald in the *British Medical Journal* (1900, vol. ii., p. 1496). Here the morphine clearly did better than anything else, and, as Mr. Fitzgerald remarks, without any sign of bad effect.

We may here call to mind the great value of morphine in relieving the uric acid headache when everything else fails; no doubt in both cases it clears the blood of uric acid as nothing else will do.

With regard to fluids, no false ideas about elimination of poisons by the kidney should induce us to deluge a patient with liquids, which only give a strong heart and obstructed capillaries the power to raise blood pressure to a dangerous height, and increase the dangerous œdema of the brain membranes.

We shall not fall into this error if we remember that uric acid controls the circulation and the excretion of water from the kidneys, while the excretion of water does not in any way control the elimination of uric acid, and also that almost the only value of purgation in these conditions is the quantity of fluid removed from the blood vessels, and the accompanying fall of general blood pressure which we can watch and measure.

The only rational treatment of cerebral hæmorrhage having an almost identical relation to high blood pressure is, it seems to me, the above purging and venesection, with starvation and withholding of fluids, many of which measures are used at present, but only in a half-hearted manner. Those who wish to succeed in bad cases must use them quickly, decidedly, and in combination, watching only their effects on blood pressure. In these cases with diminished food and the help of a little fruit I have reduced total fluids to 1 pint or even ½ pint in a week.

I believe few or no patients have ever died from undue reduction of blood pressure; while hundreds and thousands have died from its insufficient reduction.

CHAPTER VIII.

Mental Disease, Fatigue, and Syncope.

Mental depression is a concomitant symptom of the uric acid headache, and by influencing uric acid I could produce or remove it with the other symptoms (*Practitioner*, November, 1888, paper on "Mental Depression and the Excretion of Uric Acid").

The condition which accompanies the uric acid headache is one of dulness and inability for effort, either mental or bodily, with forgetfulness of names of persons and things. It is closely related on the one hand to sleepiness, and on the other to a mental disposition to take the worst possible view. In this condition self-reliance is gone, a feather weight will crush to the dust, and the greatest good fortune will fail to cheer.

A considerable amount of irritability and bad temper will be manifested, so that those around a sufferer are soon able to diagnose the condition for themselves.

I believe that mental depression is occasioned by a slighter grade of the same condition that produces the uric acid headache; that is to say, by a less intense collæmia, or by collæmia associated with debility or weakness of the heart, which prevent the great rise of blood pressure which occasions the headache. While I now rarely or never have enough uric acid to produce a bad headache, I still occasionally have enough to produce some irritability and mental depression, though this also is slight in comparison.

All those who call themselves nervous or are said to suffer from nervousness and who are suffering from mixed conditions of anxiety and depression, will be found to have a slow collæmic circulation with its various consequences. Nervousness is known to be often associated with rheumatism; when the uric acid is in the joints and fibrous tissues patients are rheumatic, but relatively strong in nerve;

but when it is in the blood interfering with the circulation in the brain, they are no longer rheumatic, but are depressed and nervous.

Clear the blood of uric acid by any of the drugs producing retention, and as blood pressure falls, the pulse rate quickens, the urine increases, the mental condition alters, ideas flash through the brain, exercise of mind and body is a pleasure, the impossible is within reach, and misfortunes slide like water off a duck's back. To such a terrible extent are we the creatures of the circulation in the brain.

Some assert that men seek for oblivion when they take opium, cocaine, &c. I believe this to be an error. I would exchange an eternity of oblivion for one hour with my cerebral circulation free from uric acid. Opium or cocaine will free it, and are therefore sought.

In all cases the cause of the misery is central (the circulation in the brain), but the mind, perturbed in its action, seizes first on one subject and then on another about which to worry itself. While the bad circulation continues, these sorrows are just as real to the sufferer as if they arose from serious external conditions.

Soon after my first paper on mental depression (*Practitioner*, previous reference), Professor Lange, of Copenhagen, kindly sent me a monograph which he published in 1886 on periodical depression and its connection with the uric acid diathesis (*Om Periodische Depressions Zustände, Cobenhavn*, 1886).

His clinical observations and treatment ran parallel to my own, but he knew at that time nothing about the relation of the disturbance of function to collæmia, and merely treated the uric acid diathesis, which he had found by clinical observation to be related to this periodical depression.

His observations and clinical experience confirm my own, but he had not grasped the real pathology of the trouble.

In a review of some of my researches on uric acid, Dr. G. Hoffmann (*Prager Med. Woch.*, 1889, No. 28) mentioned, in reference to my assertion that acids cleared the blood of uric acid and produced a condition of mental brilliancy, that there is a proverb current of which he speaks as follows: "Es ist ganz merkwürdig dass in Westböhmen, vielleicht auch anderswo, das Volk den sauren Speisen einen günstigen Einfluss auf die Gemüthsstimmung zusschreibt; wenigstens ist dort das Sprichwort, 'saur macht lustig gang und gäbe.'" This is exactly my experience, and acids do it by affecting uric acid.

Blood pressure is directly proportional to the amount of uric acid

circulating in the blood, but blood pressure means, and is due to, obstruction of capillaries; therefore obstruction of capillaries is proportional to the amount of uric acid in the blood.

Obstruction of the capillaries in the brain means, probably, stasis and hyperæmia in the brain. Therefore, *ceteris paribus*, stasis and hyperæmia in the brain are proportional to the uric acid in the blood.

In mental activity and excitement the brain is large and its cortex hyperæmic, and under opposite conditions relatively small and anæmic. It is also anæmic in sleep.

Dr. S. G. Burnett, in a lecture on "The Diagnosis of Incipient Melancholia" (*New York Medical Journal*, May, 1891, p. 497), says: "In melancholia there is a dejected and subdued appearance with decreased activity of mind and body, slow defective mental reflexes, and a delirium of self-reproach and persecution. Meynert believes the symptoms found in melancholia are the result of an anæmic condition of the cerebral cortex. Clinically we know that an abnormally anæmic condition of any organ means starvation, followed by a decrease and change in function, and if continued long enough the condition must become degenerative in character." It seems probable that stasis and hyperæmia affect, in the same way as anæmia, the interchanges between the blood and the tissues of the brain; hence their effects are similar or identical.

Among symptoms of incipient melancholia this writer lays stress upon pain in the back of the neck (nuchalalgia), insomnia and mental depression. From this description of nuchalalgia it seems to be identical with my uric acid headache, which, when severe, is right in the centre of the occiput, just above the insertion of the ligamentum nuchæ. About insomnia accompanied by high tension Sir W. H. Broadbent and others have written.

It seems probable that when insomnia is associated with high blood pressure the cerebral arteries are distended (just as the arteriometer shows the radial artery to be under similar conditions), and are unable to shut off the blood to the extent required to produce the anæmia of sleep. But the moment the pressure is reduced by a drug like calomel, sleep supervenes, and this effect is often so marked that patients may scarcely believe they have not been given a dose of opium. Indeed, the soporific effects of opium may be due at least in part to its power of lowering blood pressure. It is interesting that collæmic sufferers from insomnia complain not that they do not get to sleep in the p.m. hours when collæmia is slight, but that they wake in the early a.m. hours, when collæmia is most likely

to be severe, and cannot again get to sleep. The proper diet treatment of collæmia has in such cases been most successful.

The great point about mental depression due to uric acid is that it is periodic, in which it resembles the uric acid headache and the fits due to the same cause. Where depression is chronic with little fluctuation, it is more probably due to morbus cordis or other organic cause, than to uric acid, though this may intensify the effects of organic disease.

We have then a condition of mental depression, between which and melancholia with delusions I agree with Sir W. H. Broadbent in believing that there is no absolute line of demarcation (see Croonian Lectures, 1887). This depression is due to a certain amount of stasis and hyperæmia in the brain produced by high blood pressure resulting from excess of uric acid in the blood (collæmia). The depression should bear the same relation to the excretion of uric acid as other diseases of which I have spoken, and the factors influencing uric acid should be of account here.

In physiological conditions we have evidence that there is more uric acid in the urine, and in the blood in the alkaline tides of the day than at night, that the excretion of uric acid is relatively greater in the summer than in the winter, and that consequently there is more in the blood in the former than in the latter (see figs. 3 and 4).

Therefore, mental depression due to uric acid should be worse in the morning hours and in the spring and summer. A good many are also distinctly worse during the afternoon alkaline tide, about afternoon tea time; and a fact of interest was brought to my notice by an intelligent patient, who found that if he took a cold bath in the morning, afternoon depression was always worse. He was advised by the late Dr. Todd, of King's College Hospital, to give this up, and he then found he was relatively free from depression in the afternoon.

Dr. Todd had evidently found out empirically that mental depression in the afternoon was sometimes a result of a morning cold bath, a matter there is now no difficulty in understanding. For it is obvious that if the cold bath and the exertion of taking it acted as stimulants to nutrition, causing a rise of urea and acidity, they would diminish the excretion of uric acid in the morning, and the amount so held back would probably pass through the blood in the afternoon alkaline tide (as in the artificial headache, chapter vi.), and account for the observed increase of depression. A warm bath on the other hand would increase excretion in the morning and leave less for the afternoon, and in the same way some

exercise with perspiration in the early morning hours will increase the quantity of uric acid excreted in those hours (see fig. 46); there will be little left, for afternoon excretion and well-being may take the place of the usual depression (see also fig. 40).

In my first paper in the *Practitioner* I noted that in France the July suicides far outnumber those in any other month, and suggested that the effect of season on the excretion of uric acid might give a simple explanation. I see some French statistics quoted in the *Lancet*, 1893, vol. i., p. 1413, show that of all suicides 31 per cent. occur in spring, 26 per cent. in summer, 21 per cent. in autumn, and 22 per cent. in winter. Probably the autumn (the first cold after the plus excretion in the summer) furnishes the lowest urate excretion of the year, just as spring (the first warmth after the retention of the cold season) furnishes the largest urate excretion (fig. 4). I note also that Sir John Sibbald is reported as saying (*British Medical Journal*, 1900, vol. i., p. 497: "The gradual rise in the suicide rate from the months of November, December and January to the months of May, June and July, and the gradual fall after these summer months, is one of the most remarkable facts in vital statistics, the proportional progress from month to month being almost identical for all countries north of the equator." Doubtless south of the equator the suicide rate of the months is reversed, and the effects of temperature on the solubility of uric acid in the blood will some day be acknowledged to give the only complete explanation of the facts.

I also believe, and have collected records of such cases that suicide is more often committed in those hours of the day when the excretion of uric acid and collæmia are greatest.

I obtained cuttings of all the cases of suicide in the daily and weekly papers for about twenty days, at the end of March and beginning of April of 1894.

The total number thus tabulated was 99, but four were recorded so indefinitely that nothing could be said as to the hour.

Of the remaining 95 cases, in 66 the hour was definitely stated, but in 29 it was only given as morning, afternoon, evening or night.

Now, on dividing the 24 hours into two parts, from 5 a.m. to 5 p.m., and from 5 p.m. to 5 a.m., we get probably the largest excretion of uric acid in the 12 hours, 5 a.m. to 5 p.m., and the smallest excretion in the 12 hours, 5 p.m. to 5 a.m. (see figs. 1, 2, 3 and 38).

Taking the 66 cases in which the hour of the fatal act is

definitely stated, we get in the 12 hours 5 a.m. to 5 p.m. 37, and in the other 12 hours 29.

Of the 29 less definitely stated cases, 14 were in the morning, 9 in the afternoon, 5 in the evening and 1 in the night, and here again is a preponderance of alkaline tide hours.

I should not expect more than a preponderance in the normal collæmia hours, because we are here comparing pathology with physiology; and when digestion has been thoroughly upset, plus excretion with collæmia and consequent depression may continue through the 24 hours.

Some interesting facts have appeared in the medical papers; thus in the *Lancet* of July 28, 1894, the Paris correspondent gives notes of an epidemic of suicide then occurring in France, in which he points out that it coincides with the onset of hot weather, and that the fatal act appears to be most often committed between the hours of 6 a.m. and 12 noon.

In a letter to the *Lancet*, August 11, 1894, I showed that gout, which corresponds with retention of uric acid and its absence from the blood, affects exactly the opposite poles both of the day and year, being at its worst in the evening hours and at its best in the morning hours, and (on the authority of Sydenham) worst in February and best in the warm months.

The *Lancet* of August 17, 1895, has an annotation in which they refer to my letter and acknowledge that my suggestions are helpful; but they end with the conclusion that suicide is due to moral failure, and is not to any great extent connected with physical conditions.

This is a conclusion which appears to me to be absolutely wrong, and against the weight of evidence. Why does moral failure show seasonal variations?

In my own experience of mental depression I find it so insidious in its onset that, even knowing what I do of its collæmic causes, I have the utmost difficulty in realising that things are not really all wrong, and that a mere dose of calomel will make them seem bright. And if I am thus deceived, how much more those who understand nothing of physical causation? The final cause of suicide is usually some apparent trifle which however appears at the time a terrible reality to the sufferer.

As to moral sense, reason and resolution, they simply do not exist in such conditions.

A man is in fact temporarily insane, and differs only in degree, not in kind, from the habitual inmate of an asylum. The one is held to be morally irresponsible. The other, according to the *Lancet*, is

not so. I feel sure that greater knowledge will compel us to a different view.

In the *British Medical Journal*, 1895, vol. i., p. 378, it is pointed out that suicides are most frequent between 45 and 55, this being exactly the age at which metabolism and nutrition begin to slacken, and the uric acid stored up in previous years to pass through the blood. These also are the years in which high blood pressure and its results—sleeplessness, mental depression, causeless worry, chronic Bright's disease, and cerebral hæmorrhage begin to be troublesome.

In my opinion these mental and physical diseases cannot be treated apart. Those who before the fatal act were sleepless, unhappy, and worried about trifles, were suffering from well-marked disease of the circulation, and should have received definite treatment in addition to moral suasion.

The fact that suicide shows marked fluctuations corresponding with the daily and yearly fluctuations in the excretion of uric acid proves that it is intimately connected with collæmia, but I do not deny that there are often organic factors as well, *e.g.*, morbus cordis or visceral diseases, and yet the uric acid may to some extent determine the result and its time relations.

I believe also that the irritability and bad temper of collæmia, due to the stasis and hyperæmia it brings about, may account for a certain number of murders. They also have a seasonal variation, and May, indeed, has been called the month of suicides and murders (*Lancet*, 1890, vol. i., p. 1208).

May is one of the first months in which there is decided warmth, and with the falling acidity some of the uric acid retained in the winter begins to be dissolved in the blood, and more or less marked collæmia results.

I believe the above-mentioned physiological fluctuation in the excretion of uric acid, and the concomitant collæmia, account for the observed fluctuations in the incidence of mental depression, suicide and murder. In the *British Medical Journal*, 1897, vol. i., p. 392, there is the record of a case in which stupor cleared up completely on the supervention of a little febrile movement, and this is regarded by the observer as curious, but if we bear in mind that fever cures collæmia, there is nothing curious about it.

I brought some of these points to the notice of the British Medical Association Meeting in Edinburgh in 1898, my paper on "Suicide as a Result of Error of Diet" being published in the Journal in September of that year. A summary of it may be useful.

There is a daily high tide of uric acid in the blood in the a.m.

hours, and a low tide in the p.m. hours, due to the solubility of uric acid and dependent on the varying alkalinity of the blood, which in its turn is governed by hours for meals and the acid or alkaline foods taken. In the a.m. hours (without food) alkalinity is high. In the evening (after the daily meals) alkalinity is low. By reversing meal hours, and altering foods, the alkalinity of the blood can be altered, and the same can be done with drugs. Uric acid with its effects and symptoms will follow this lead. There are daily secondary waves of *plus* uric acid due to cold, heat, altered food hours, &c., and if a *plus* wave surcharges the large morning excretion, pathological depression ensues. If a *minus* wave is added to the low evening tide marked well-being supervenes.

The excretion of uric acid is generally an index of the amount in the blood. There is a corresponding annual high tide of uric acid in spring and summer (because (1) blood alkalinity is increased by heat, and (2) heat is a direct solvent); and an annual low tide in autumn and winter (because (1) cold diminishes alkalinity, and (2) cold is a direct precipitant). The seasonal variations thus correspond with the daily. When accidental, diurnal and seasonal waves coincide and flood the blood with retained uric acid very serious pathological results may occur.

In the *Lancet*, 1904, vol. i., p. 1141, there is an annotation on spring slackness: "Who does not know the enervating sense that accompanies the first warm day of the year?" My reply would be: Those do not feel it who have avoided the introduction of uric acid, and have in addition taken precautions against cold, which would otherwise cause retention during the winter months. I have also noted an observation by Dr. W. R. Dawson in the *Medical Press*, 1904, vol. i., p. 469, on "Glycosuria and Insanity," which he associates with depressed states of mind, so that eight of twelve cases will either be melancholy or more or less depressed. Finally he points out that in nine of the cases the glycosuria commenced in the months of May or June, and in the tenth the second appearance took place in May. This is all simple; there is but one cause of spring slackness, of depression and of glycosuria, and they all occur in the spring, because they are results of the same cause.

In the *Lancet*, 1905, vol. i., p. 222, Dr. J. W. Russell discusses atmospheric conditions and cerebral hæmorrhage, in which he shows that there is a tendency to cerebral hæmorrhage on days of high atmospheric pressure, and that a rising thermometer increases this effect. I know that a uric acid headache, which is tolerable in a house two or three storeys above ground, becomes decidedly worse

on descending to the level of the Central London Railway. The rise of atmospheric pressure obviously increases the blood pressure, and the increase of temperature favours the passage of an increased amount of uric acid into the blood. Hence such a rise of temperature and pressure might just suffice to precipitate a cerebral hæmorrhage in those on the verge.

Climacterical Fluctuations.—Similarly there are life fluctuations. (1) A retention or minus excretion of uric acid during the rapid development of youth, because a large nitrogenous metabolism means high acidity of the urine and low alkalinity of the blood. This is followed by a corresponding *plus* excretion when the rapid development and metabolism end. (2) A retention smaller but of longer duration in the high nutrition of strength and maturity, this being specially marked in those who take beer or wine; and this also is followed by a *plus* excretion, as nutrition and activity fail with advancing old age, and the urates which caused gout in the joints in previous years now cause high blood pressure, mental depression, anæmia, and gravel of declining years. The blood decimal gives an exact indication of these fluctuations, so that a glance at the mucous membranes is often sufficient to indicate the uric acid history of several months or years. Thus the decimal is high, ·9, in the rapid development of youth and falls as this ceases, as is best seen in the chlorosis of girls, ·5; though boys often come down to ·7. It rises later with the high nutrition of maturity to ·8 or ·9, only to fall again with old age to ·7 or below it (see chapters v. and xii.).

Influence of Hour, Season, and Food on Suicide.—Suicide appears to be less frequent in warmer countries and more frequent in cold; and though it is difficult to distinguish between the direct dietetic and climatic effects, it is probable that in countries with the longest and coldest winters there will be most retention of uric acid, and consequently most excretion in the following spring and summer, with its result depression and suicide. Among countries of similar temperature, such as England and Scotland, there is more suicide in the former, where most meat is taken and beer is drunk, and less in the latter, where less meat is taken and the beverage is whisky, which is not acid. The same applies to the pathology and causation of gout. Suicide is believed to be increasing in England, and so is the meat eaten per head; and suicide is most frequent in and near large towns, where the supply of meat is greater. It appears to increase with civilisation and culture, but these tend to go with towns and meat-eating, and those who use their brains are generally led to do so because they have better powers than others, and this

better power may depend upon large cerebral arteries more easily affected by high blood pressure, as I have pointed out in the case of migraine (the uric acid headache) and mental depression.

Suicide and Sex.—The great preponderance of suicide in males may be due to several factors: (1) That men are more exposed to weather than women, and exposure may be equivalent to living in a colder climate, which we have already mentioned (see also fig. 40). (2) Men eat more meat than women. (3) Women excrete large quantities of uric acid at or just after the monthly period, so that, other things being equal, they will have less retention and accumulation. But this monthly *plus* excretion accounts for the fact that when they do commit suicide, it is often at the monthly period. Again, women suffer much less than men from gout on the one hand and stone and gravel on the other. In the same way life fluctuations explain why women suffer more than men from 15 to 20 years of age. The uric acid stored or retained in the rapid nutrition of girls about 13 or 14 which ends about 16 or 17, passes through the blood about and after these latter ages, and accounts for the blood and circulation changes ending in chlorosis, headaches, depression, epilepsy, or suicide. On the opposite side is the rapid nutrition and retention of uric acid at 13, with its acute rheumatism; in such girls we often get a complete alternation of rheumatism and anæmia, with headache, epilepsy, depression, and suicide as more occasional consequences.

Influence of Age.—A similar fluctuation explains the increase of suicide with oncoming old age (from 45 to 65), the uric acid then coming through the blood being the result of the meat and beer of the high nutrition of maturity; and here also mental depression and suicide are associated with the effects on the blood (anæmia), and on the urine (gravel and stone); thus the gout of 45 is related to the anæmia of 65, as the rheumatism of 13 is to the chlorosis of 17, and the suicide of 65 has a similar causation with that of 17.

Influence of Occupation.—The effect of sedentary occupations in increasing suicides is simple, since, if other things be equal, the well-nourished sedentary will retain more uric acid, for exercise increases the alkalinity of the blood, so that sedentary occupations range with cold climates. The effect of alcohol is again the effect of meat, for alcohol is generally taken to relieve the depression meat produces; and if meat is discarded alcohol is no longer required. The effect of a military life is probably mixed, but we may remember that a Scotch or Irish peasant lad who has been accustomed to get animal flesh about once a week is put, on joining the army, on to meat once a day or oftener.

Influence of Fever.—During the rising temperature of the onset of the fever there is considerable retention of uric acid from diminished alkalinity of the blood, and when later on the fever comes to an end and the alkalinity rises, the retained uric acid passes into the blood in excess, and more or less depression of body and mind results. Thus influenza, pneumonia, other fevers, a shock or injury, may cause post-febrile collæmia and depression.

Influence of Pregnancy.—Similarly, pregnancy when normal and accompanied by active metabolism and increase of nutritive activity, produces some retention of uric acid; and when nutrition is upset by vomiting and other disturbances of parturition, the blood is seen to be flooded with much of the retained uric acid, and homicidal or suicidal mania may result. Pregnancy has parallel effects on headache, epilepsy and other diseases related to uric acid in the same way as mental depression and suicide.

Weather and Season.—Suicide is at its worst in the warm months when gout is less frequent, or at its best in chronic sufferers; and suicide is at its best in cold months, when gout is most frequent. Indeed, the very uric acid causing gout in winter may cause suicide in the following spring or summer. Cases in which mental depression disappears on the supervention of an attack of gout are common, so that I have suggested that in similar cases treatment should be directed to producing an attack of gout.

If a person feels languid when the weather is hot it is a proof that there is some excess of uric acid, for persons free from uric acid feel better and stronger in hot weather. This feeling of increased strength is due to the fact that a large part of our nourishment is required to keep up the temperature of the body, and when the weather is hot less is required for this purpose and more nourishment, and consequently more force, are available for other purposes.

When in Cairo I noticed an Arab wrapping his cloak round him and apparently suffering from the effects of cold in a temperature above 60°, and on my remarking that I found it hot enough, he replied that he loved the sun, for it made him strong. Being a big, strong man he had something on which to speak.

The Arab takes little uric acid, for three-fourths of the year he is more or less constantly exposed to a high temperature, and he therefore excretes daily practically all the uric acid formed and swallowed. Consequently, when the weather begins to be hot, there is little or none retained, and therefore the sun, which diminishes the amount of work required to keep up his temperature, leaves him plenty of power for external work and encourages a feeling of strength unhindered by lethargic feelings of collæmia.

Natives of the warmer parts of South America assert that though they can eat meat when they are at home with comparative impunity, they are not able to eat it with anything like similar impunity in this country, in consequence of depression and other troubles. Probably a similar explanation can be given. In their own country it is hot; they swallow some uric acid in meat, but it passes out daily as they swallow it, and in the heat it is not only eliminated, but, in passing through the blood, it is held in good solution by the heat and available alkali. Doubtless it causes some anæmia in its passage, but otherwise it has comparatively little bad effect. In this country, however, temperature does not favour the complete solubility of the uric acid, and greater disturbances of circulation occur as it is excreted, and there is a greater tendency to accumulate and retain some of it.

Bright's Disease.—This has an important relation to suicide, and is the disease of all others in which a considerable excess of uric acid in the blood is most constantly met with.

Drugs.—The relation of suicide to drugs results from the similar fluctuations in uric acid excretion which they produce. Thus people who indulge in opium, cocaine, alcohol, tobacco, chloroform, or ether, may greatly increase the retention of uric acid (and therefore the amount available for future collæmia) entailing circulatory and mental changes. Contact in certain trades with metals, such as lead and mercury, may act in the same way.

Those, however, who take drugs which produce solution and elimination, will be more than usually free from collæmia. The only freedom from uric acid is to be obtained by swallowing none, and by eliminating freely all that the body forms.

Most authorities agree on two points: (1) That suicide is increasing in Europe and America; and (2) that its incidence bears everywhere some relation to warmth and season.

I would point to the concomitant increase of meat eating and tea drinking as the best evidence of the causation to which everything seems to me to point.

As regards season, its effects on collæmia and the excretion of uric acid are the only explanations in the field.

The *Lancet* offered another interesting annotation (*Lancet*, 1899, vol. ii., p. 289) in which it quoted authorities to the effect that the increase of suicide is due to the strain of modern life, decadence of orthodox religious belief (especially in cities) and other mental and moral causes.

These things, far from being the causes of suicide, are co-results

of collæmia and the defective circulation and nutrition induced in the great nerve centres. It is easy to show that they all disappear with the removal of the bad circulation.

To me it has long seemed that the cerebral circulation controls the whole being and doing of man, and that diet controls to a large extent the cerebral circulation.

Diet.—The relation of suicide to diet is that while sufficient albumens for nutrition may be taken without fear, if these albumens are got from animal flesh, there will be direct introduction of uric acid, and if tea is added this will be increased, while if unnecessary albumen is taken there will be excessive formation of uric acid, and with either excessive introduction or formation there will be storage or retention furnishing supplies of poison for future symptoms and results. Suicide is due to errors of diet which may be either those of quality (meat and tea), or those of quantity (excess of albumens above those required for the proper nutrition of the body), so that too much uric acid and too much urea are formed, some of the former being retained.

Conclusion.—Mistaken diet is one cause of suicide, and in scientific revision of diet lies hope of prevention. This justifies a hopeful prognosis, for it is possible by diet to control the uric acid in the body. I can produce or remove this mental depression at any time, just as I can produce or remove the uric acid headache and the accompanying slow high tension pulse.

Supposing I suffer from mental depression I can remove it by a dose of morphine, say gr. $\frac{1}{6}$, and I follow this by several gr. xv. doses of salicylate of soda, which eliminates uric acid best when the acidity is high.

The uric acid, held back by the morphine, is eliminated by the salicylate; there is, therefore, no collæmia next morning, and no necessity for more morphine.

The explanation of the action of diet is found in the fact that meat is a stimulant, for its first action is to clear the blood of uric acid, and all substances that produce this effect are stimulants.

Like all the other stimulants it produces depression later on when the retained uric acid passes again into the circulation. Hence stimulant taking in one form or another is an inevitable result of meat eating, and here originates the demand for tea, coffee, alcohol, morphine, cocaine, to counteract the secondary depressing effects of the original stimulant.

It follows that there is no escape from this vicious circle but the complete abandonment of meat and all the stimulants that have been brought into use by it.

In pathology the conditions which produce mental depression are just those which bring about collæmia; such conditions, for instance, as loss of employment with deficient food, functional or organic disease interfering with digestion and nutrition; anything in fact that diminishes nitrogenous metabolism and excretion of urea, for acidity falls with urea. A man in good work eats freely of meat and drinks 4d. ale; as a result his acidity rules high, hence he excretes uric acid in relation to urea of 1—40 or 1—50; that is, the excretion of uric acid falls short of formation and introduction, and he daily stores or retains a certain quantity. Now come bad times —he is out of work, can afford no beer, and little meat; urea and acidity fall, and the uric acid previously retained begins to pass into the blood and urine; there is collæmia with slow high tension pulse and mental depression, and his wife tells you he is fretting because he has no work. Clear the uric acid out of his blood, and he will cease to fret though the circumstances are the same.

Most fevers, especially short sharp fevers, such as influenza, pneumonia, scarlet fever, erysipelas, produce material for more or less intense collæmia.

It is well known that fevers raise the acidity of the urine, and I have mentioned on p. 38 a good instance of this recorded by Sir W. Roberts. When the fever comes to an end acidity falls, the uric acid is dissolved out and collæmia results.

Such collæmia will be proportional to the amount of uric acid retained, which may be reinforced by any uric acid previously stored in the body, or introduced during the fever by beef tea and meat extracts. Hence, in the convalescence of acute fevers, there will be more or less collæmia, which will continue until the stores of uric acid have been swept out, or acidity again rises with improving nutrition. Until one of these things happens there will be daily collæmia with slow high tension pulse and mental depression. This is no doubt the cause of the slow high tension pulse so common during the first few days after the crisis of a pneumonia and other fevers—a condition described by Riegel (*Zeits. für Klin. Med.*, 1890), and others as post-febrile bradycardia (see p. 200).

I have little doubt that the increase of suicide in this and other countries following epidemics of influenza (see *Lancet*, 1894, vol. ii., p. 445) was due to such post-febrile collæmia, and that this had been increased by the treatment of influenza as a depressing disease, with a free allowance of wine and beef tea.

I have mentioned two cases of pneumonia under my care simultaneously: one a powerful man, the other a weak and ill-nourished

woman ; in the former the post-febrile conditions, including bradycardia, were very prominent, in the latter very slight, and the difference was due to the fact that the man with his large metabolism of nitrogen stored much urate at the time of the fever, while the ill-nourished woman stored little, therefore the post-febrile symptoms were proportional in each case to the amount of urate passing through the blood (post-febrile collæmia).

This man also presented another interesting symptom, for during the fever of pneumonia he had no albuminuria, but on the first day of subnormal temperature (when the symptoms of collæmia were marked) he had a trace of albumen in his urine. I have no doubt that this albuminuria had an identical causation with that accompanying migraine or epilepsy, or with paroxysmal hæmoglobinuria from which it differs merely in degree. I believe an albuminuria similarly produced occurs in the post-febrile period of not a few acute diseases, and that if the post-febrile collæmia is severe and prolonged it may pass into actual Bright's disease, with which it is identical in causation. This actually occurs after some cases of scarlet fever, and we shall see (chapter xiii.) that the use of salicylates during the fever, which would, no doubt, eliminate much of the uric acid and so prevent severe post-febrile collæmia, has been thought by some to prevent the subsequent onset of albuminuria and Bright's disease (see the facts of fatigue, the effects of uric acid on the formation and excretion of urea, and the arguments in chapters xii. and xiii.).

Bright's disease is frequently associated with suicide, and in Bright's disease there is chronic collæmia, with obstructed capillaries and slow high tension pulse.

Menstruation might have been mentioned under physiology, but in menstruation there is often collæmia, because this condition is commonly accompanied with some disturbance of digestion, failure of nutrition, and fall of acidity (see figs. 31 and 32). I have already (chapters vi. and vii.) pointed out that women who have fits or the uric acid headache nearly always suffer from attacks at the catamenial period. Sir W. H. Broadbent has remarked that the pulse is often slow and of high tension in menstruation, and Dr. Barnes (*Brit. Med. Journ.*, 1890. vol. i., p. 1401) has pointed out that museums can easily be stocked with the organs of menstruating women because they so often commit suicide, and we have here again convincing proof of the connection between suicide and collæmia.

At this point we certainly touch a wide field in psychology which

we may be able to cultivate to some purpose; for the question presents itself, how far is the bias of women towards religion, and their general disposition to take serious views on matters which men often regard lightly, due to the more or less continued effects of uric acid on their blood pressure and cerebral circulation. In attempting to answer this question we must remember that depression breeds depression, that once there is an excess of uric acid in the blood this continually tends to depress both metabolism and nutrition and keep them low.

In several papers I have mentioned the experiments of Drs. Roy and Sherrington, showing that injection of acids into the veins produces enlargement and hyperæmia of the brain (*Journal of Physiology*, vol. xi., p. 85), and have suggested that the acids really affected the vessels and brain circulation indirectly by their action on uric acid.

Roy and Sherrington found also that alkalies diminished the blood in and reduced the volume of the brain; and here we have, I think, demonstrated the effects which I can produce on the circulation of the brain, and therefore on the mental condition, by influencing uric acid.

By giving alkalies I produce collæmia with slow high tension pulse, obstructed capillaries in skin, lungs and kidneys, slow capillary reflux, stasis and hyperæmia of the brain and mental depression; by giving acids I free the blood from uric acid, free the capillaries, cause a good circulation in the brain with mental brightness and well-being.

If it is objected that the action of the acid in these experiments is too quick for it to have acted indirectly on uric acid, I reply that in chemistry a precipitate occurs the moment a precipitant is added to a solution, and I fail to see why it should be delayed in the blood in which the action is probably very similar. In Mr. Saul's experiments (previously referred to), colloid uric acid is at once thrown down when the solution is acidified. Well-marked effects on the circulation can be produced in a few minutes by means of drugs taken by the mouth, and it is not surprising if the same drugs produce effects in a few seconds when directly injected; nor is there, I think, anything here to suggest that an acid acts directly on the vessels when injected, and indirectly on uric acid when swallowed, producing the same results in both cases.

Much has been written about formic acid and its power of producing endurance and strength. I tried some, but saw nothing in the results obtained, or in those described by others to suggest

any effect differing from that of other acids. Dose for dose, it may be more powerful than some.

I see in the *Lancet*, vol. ii., 1905, p. 807, an interesting annotation on the use of formic acid in the treatment of tremor, but tremor may be the sign of defective circulation in the nerve centres produced by uric acid collæmia; chorea, which is mentioned in the *Lancet* as another disease in which the acid is useful, may be another result of uric acid collæmia.

Roy and Sherrington further point out that the intravenous injection of opium but slightly affected the circulation of the brain, and yet it is easy to show that it has a powerful effect on the capillary circulation of the whole body, and also on the mental condition, when swallowed. How explain such different effects with opium, while acids have much the same whether injected or swallowed? From the point of view of uric acid causation the matter is simple enough, for opium has no direct effect on the solubility of uric acid, in which point it differs from acids and alkalies.

The indirect effect of opium is, as I have stated (*British Medical Journal*, 1889, vol. ii.), probably entirely due to its action on peristalsis. By slowing down peristalsis and the passage of the contents of the large intestine, it promotes the absorption of acid fluids from that part of the alimentary canal, and thus raises the acidity of the urine and diminishes the alkalinity of the blood. But if from any cause it fails to check peristalsis and raise acidity, it also fails to affect the capillary circulation, and will then produce neither mental well-being nor absence of fatigue. We must remember that belladonna (fig. 9), which has an almost opposite effect on the intestines has also an opposite effect on the solubility of uric acid, and so on nutrition and function.

Now, opium may fail to raise the acidity of the urine from several causes, such as the presence of much alkali in the food, or where there is dyspepsia with vomiting and diarrhœa, which must be overcome before acidity can be raised.

For this reason I believe opium has less power, dose for dose, over the vegetarian native of India than over the meat-eating native of these islands. Its action in myself is certainly far less powerful now that I take almost nothing but cereals, fruits, and vegetables.

I should otherwise have given curves showing the effects of opium on fatigue and the excretion of urea, but to do this rather large doses of opium would be required, and I therefore selected calomel, which acts directly on uric acid, and is independent of acidity (see fig. 48).

Small doses of opium do not raise the acidity of my urine to any marked extent, and do not therefore clear the blood of uric acid or cause well-being and absence of fatigue except to an extent insufficient to show well in curves: but there is no doubt that opium, cocaine, and other drugs well known and commonly used to diminish or prevent fatigue act as calomel does by clearing the blood of uric acid, so that the vessels are free and there is consequently a good circulation through the muscles with prompt elimination of urea and active metabolism. But when, as in my case, they fail for the reasons given above to affect the solubility of uric acid to any marked extent, they also fail proportionately to affect fatigue and excretion of urea. If it is urged that acids relax and alkalies astringe the capillaries directly, I reply that in the human subject if you remove all available uric acid, alkalies will not raise blood pressure, because they do not produce collæmia. Again, lithia markedly diminishes the acidity of the urine, but yet it does not produce either mental depression or scanty urine; on the contrary, it causes well-being and diuresis (see pp. 58 and 186), and the excretion of uric acid tells us why, for in place of producing collæmia as soda and potash do, it clears it out of the blood and diminishes its excretion.

Lead, iron, and a number of other metals cause retention of uric acid, and during this action produce also free capillaries, quick capillary reflux, well-being and diuresis. Everything that clears the blood of uric acid causes diuresis if there is available water in the blood; and conversely almost every diuretic, in the pharmacopœia and out of it, is found on investigation to clear the blood and urine of uric acid. I have shown that all these substances produce the same effects on uric acid; from the other point of view it would have to be shown that they all separately produced the same effects on the arterioles or capillaries.

In a word, all the phenomena are proportionate to the uric acid, and not to the drugs which only act indirectly upon it.

My experience of the effects of diet in my own case (though it by no means stands alone) is sufficient to prove this, for if alkalies contract the arterioles of the brain and produce anæmia, depression, headache, &c., I should be much worse on a milk and farinaceous diet, which has greatly diminished the acidity of my urine; whereas I am much better and have not a tenth part of the former headache, high blood pressure, and depression. Many of my patients have had similar experience. Severe collæmia is now impossible, hence its effects disappear, but alkalies are plentiful in the circulation, and have no effect on the capillaries.

Experience has convinced me that the best way to keep the brain circulation free from uric acid is not to dose it with opium or cocaine, which, while clearing the blood to-day, store up the poison for future trouble, but to reduce formation and introduction of uric acid, and to provide for its constant free excretion by a plentiful supply of alkali in the shape of such fruits as apples, and such vegetables as potatoes. In winter it is necessary to clothe fairly warmly and otherwise to guard against the too prolonged action of cold, as this tends to raise acidity and cause retention of urates, especially when its action is aided by a diet relatively poor in the above-named fruits and vegetables (see remarks on fig. 74).

I am here speaking of functional, temporary, periodical depression, though I believe if the vascular conditions that produce it are very often repeated over long periods they may at last bring about irremediable organic changes. I have, nevertheless, been able to effect great improvement in periodic depression, which had lasted through many years by alterations in diet.

There is probably no fact more widely recognised than that mental irritability and depression are relieved by the smoking of tobacco. If we look up tobacco in a system of therapeutics we find it classed with the depresso-motors, *i.e.*, with the drugs that diminish muscular power and enfeeble the heart, whilst among drugs having a similar action it is interesting to note that ipecacuanha and antimony are also efficacious in migraine.

It has been pointed out by several observers that smoking diminishes intellectual power (see letter by Dr. C. R. Drysdale in the *British Medical Journal*, 1896, vol. ii., p. 233, and references there given), and if it in any way weakens the power of the heart it is easy to see how it may hinder due nutrition and development of the brain. I am indebted to Dr. Morgan Dockrell for the information that tobacco may precipitate alopecia senilis, but that the hair may recover if smoking is stopped, so that it apparently affects nutrition on both sides of the skull.

My observations on tobacco smoking as affecting the pulse show that it lowers blood pressure, and quickens the rate of the heart's action, and it is easy to understand that in accordance with Grashey's observations * it will in this way increase the volume of blood passing through the brain, and so produce well-being. This well-being is not accompanied by a desire for activity and a feeling of tone in the muscles, but rather by slight languor and disinclination for exertion.

* *Fest-Schrift Munchen* (J. F. Lehmann, 1892).

The arteriometer also records the effects of tobacco smoking, as on several occasions I have found a distinct diminution of the diameter of the radial artery after smoking for 30—40 minutes. We must not lose sight of the fact that, apart from the action of nicotine or tobacco, inhalation of the products of combustion of any vegetable matter means taking in a certain amount of the acid products of combustion such as nitrous or sulphurous acids, which may be absorbed from the mouth and nose in sufficient quantity to affect the alkalinity of the blood. So that tobacco is another instance of a substance which ministers to man's comfort like opium and cocaine by clearing his blood of uric acid, but like these also, its first action may be followed by a rebound with irritability, mental depression, and (in extreme cases) tendency to suicide (see *British Medical Journal*, 1890, vol. ii., p. 1161).

Believing that mental depression bears exactly the same relation to the excretion of urates as headache, and that their causation differs merely in degree, I was interested in hearing from one of my patients (a man of conspicuous mental ability, who had all his life suffered from mental depression), that when he had his worst attacks (in the early hours of the morning), he obtained relief by sitting upright in bed, in exactly the position that I assume in my headache. The fact is not only interesting as a parallel, but it proves, I think, that in this case mental depression was not due either to feeble heart or to cerebral anæmia.

Doubtless mental depression may be due to a weak heart and consequent cerebral anæmia, but such depression would be chronic rather than paroxysmal, and would be benefited by lying down.

It is interesting to remember that in mental depression associated with high blood pressure, digitalis does harm. I have given it in cases where there was a doubt as to the power of the heart, and have seen others do the same. The only result was to make the depression worse.

This is comprehensible, for digitalis affects both factors in the causation of high blood pressure ; it strengthens the heart and contracts the arterioles. But where mental depression is associated with real cardiac weakness and low tension digitalis may do much good. The use of the capillary dynamometer and the sphygmometer will help to distinguish the cases that need digitalis from the others.

The relation of these depression attacks to the early morning hours and the similar relation of melancholia (see *Proceedings of the Medical Society of the State of Pennsylvania*, June, 1890) are of interest in connection with the large excretion of urates and scanty

urine which characterises these hours in physiological conditions, I look upon the pathological condition as a mere exaggeration of the physiological (see figs. 1, 2 and 3).

An illuminating case is published by Dr. Willoughby Gardner in the *Lancet* (1891, vol. i., p. 1311). A patient suffers from gout attacks and gouty dyspepsia. On March 3, 1891, he has acute gout in the left foot. From this he recovers two or three days later, considers himself well, and proposes to return to work.

On Sunday, March 8, he attended three long religious services and took no exercise. On the morning of March 9 he was suffering from acute religious melancholia with delusions and threats of suicide. Pulse weak, but artery full between beats. Heart, second sound in second right intercostal space loud and ringing.

He was given a mercurial purge and mustard blister to nape of neck.

In the middle of the night he was seized with a slight attack of gout in the left foot (the same foot as before) and "at once all depression completely disappeared," the pulse felt stronger and the radial artery could not be felt between the beats; the second sound of the heart no longer accentuated or loud.

The case in terms of uric acid causation reads as follows: Gout alternating with dyspepsia, cure of an acute attack of gout, some dyspepsia and collæmia. While this is going on he sits out three long services in a cold church, and takes little exercise. This produces minus skin activity, a rise of acidity, and some retention of uric acid. Next morning, in the alkaline tide, collæmia returns reinforced by the amount retained on the Sunday (see fig. 40). This obstructs the capillaries and raises blood pressure, which in turn produces such an altered circulation in the brain that melancholia results.

A mercurial purge is given; this clears the blood of uric acid, driving it into the liver, spleen and joints, especially the centre of previous attacks, the left foot, and produces a gout attack in the night. At the same moment, the blood being cleared of uric acid, the pulse alters its character, the melancholia due to the effects of high blood pressure on the cerebral circulation clears up completely. Mercury here acts just as a dose of iron, lead or even lithia would have done, and for the same reason, for urate of mercury, like calomel and other salts, is very insoluble, so that the urate of mercury tends to be deposited especially in those joints where previous attacks had left some urate to attract it.

I am ready in such a case to undertake to produce either gout or

melancholia to order, and in other cases similar effects can be produced proportionate to the amount of urate that is at hand, and can be acted on.

It is thus easy to see why an attack of fever should restore mental health in melancholia, or why thyroid extract should be used for the same purpose (see *British Medical Journal*, 1895, vol. ii., p. 765).

I have shown in the preceding pages: (1) that mental depression is commonly associated with high blood pressure, that high blood pressure causes the depression, and that the cause of high blood pressure is uric acid collæmia acting through defective capillary circulation.

(2) That the physiological, pathological and drug action fluctuations in the quantity of uric acid in the blood and urine thus account for the more important facts about depression, melancholia and suicide.

(3) That they explain the periodicity of these disturbances, their relation to time of day and season of year, to heat, to cold, to good and bad air, to foods, drinks, exercise, clothing, to other functional or organic disease, and last, but not least, to the numerous drugs used for prevention or cure.

Mental depression which is periodic, in association with high blood pressure and slow capillary reflux, entails the treatment of uric acid collæmia, and collæmia successfully treated means restoration of normal circulation, and probably of normal brain function.

It is perhaps permissible to say that in all such disease where careful investigation of the circulation shows well-marked departure from the normal, in association with excess of uric acid in the blood and urine, collæmia should be considered, and, in the absence of other obvious organic disease, be carefully treated just as in the diseases which a knowledge of its effects has now given us power to control.

I will mention shortly a few of the more important of these diseases, and my reasons for suspecting that they may have a causal relation to collæmia.

First comes that mental condition diametrically opposed to depression, namely, excitement, delirium or mania.

This is a condition chiefly associated with fevers (as delirium), alcohol, and certain drugs, many of which (as chloroform, ether, cannabis indica) have the effect of lowering blood pressure.

Fever lowers blood pressure by clearing the blood of uric acid and freeing the capillaries; here the capillary reflux is 2, 3 or 4 half

seconds, it may be less than 2 or almost too quick to count, and the blood pressure is low because the free passage through the capillaries gives the heart little to oppose, and it quickens its rate in accordance with Marey's law.

Just as mental depression and melancholia are found in association with high blood pressure, the opposite conditions of excitement, delirium and mania are found in association with low blood pressure, which has been demonstrated by Dr. M. Craig, working with the Hill-Barnard Sphygmometer, and is recorded by him in a paper on "Blood Pressure in the Insane," *Lancet*, 1898, June 25.

But excitement or even mania may be found in patients who have no fever and have taken no drugs; in patients also whose capillary reflux is not quick, but slow, perhaps much too slow; how then does it occur?

Reverting to the first principles of the circulation given in chapter v., we shall remember that there are only two known conditions that allow of subnormal blood pressure: (1) free capillaries with a normal heart, as in fever; (2) obstructed capillaries with a weak heart, that is to say, there would be high blood pressure if the heart was equal to the work involved in keeping it up.

We now see that conditions of mental excitement, delirium, or mania, with low blood pressure, may be met with:—

(1) In fevers;

(2) As the result of taking certain drugs;

(3) In conditions of heart failure.

In fever the whole fall of blood pressure may not be due to free capillaries, there may also be a heart failure factor.

The drugs may act by clearing up collæmia and freeing the capillaries, but also by weakening the heart.

We must remember that high blood pressure is a cause of heart failure, and that when the heart fails there may be a rather rapid change from high blood pressure to low.

Hence, a patient to-day suffering from high blood pressure and mental depression, may to-morrow (from shock, injury, exposure to cold and wet, deficient food, serious illness followed by debility, and other causes), suffer from cardiac failure with low blood pressure, excitement or mania; and if you can strengthen the heart you may get rid of the mania and bring back the depression.

The full sequence of causation often seems to be as follows: A patient has high blood pressure of which for years there may have been more or less obvious signs; on this supervenes a fever or other severe illness, leaving post-febrile debility and collæmia; these conditions cause heart failure, and mania results.

After an interval the large amount of uric acid is excreted, the capillaries are less obstructed, and the heart recovers for a time; but having once failed before high blood pressure, is liable to do so again.

As the heart recovers nutrition improves, and the patient is himself, but is again retaining uric acid, and just as in paroxysmal headache and paroxysmal mental depression, a time of improvement will be followed by another outbreak. Some change in weather, climate, holiday, exercise, &c., precipitates the stored acid again into the blood, again the heart fails and again mania results, and so we get paroxysmal mania in the place of paroxysmal migraine or mental depression, because in the one case the heart fails, but in the other it does not.

In everyone blood pressure is higher in the morning and lower in the evening (see fig. 38), hence melancholics improve and maniacs grow worse as the day advances, a most interesting and instructive fact pointed out by Dr. Craig (prev. ref.).

This change in blood pressure may be simply related to the alkalinity of the blood (which is higher in the morning and lower in the evening), to the quantity of available uric acid (which is greater in the morning and less in the evening) and to diet, which introduces uric acid or withholds it. Hence, by influencing the alkalinity of the blood and the quantity of uric acid, this diurnal and other changes of blood pressure can be modified.

It does not, of course, follow from this pathology that everyone who has a serious fall of blood pressure will have delirium or mania, any more than that everyone who has high and rising blood pressure with collæmia will have headache.

There is some anatomical factor, such as the form of the skull, or the size or distribution of the vessels, which disposes one patient to suffer sooner or more severely than another, from similar changes of blood pressure, but in so far as the circulation changes are due to uric acid collæmia, the control of this will control the functional disturbances.

With regard to the action of thyroid extract, previously spoken of, and the causation of these conditions, some points are mentioned by Mr. R. R. Leeper in the *British Medical Journal* (1900, vol. i., p. 194).

A patient (female) admitted in a condition of acute mania; with careful rest in bed and the administration of digitalis her pulse rate became slower, and she sank into a semi-stuporose condition. She was then put on thyroid, and after a week the "tachycardia commenced to return, and with it came back her intelligence."

Further on Mr. Leeper remarks with regard to the effects of the treatment:—

"The administration of thyroid extract owes its remedial results to its direct stimulation of the cortex, and the increased metabolism thereby induced among its elements. The rise of temperature is, however, not the most constant symptom of reaction. To the increased pulse-rate and quickened circulation must presumably be attributed most of the good effects of the treatment."

I can explain every fact here mentioned: the patient was maniacal on admission because the heart had failed before high blood pressure; the capillary reflux would have been found slow, and yet the blood pressure was subnormal (cardiac failure).

With rest, digitalis and stimulants, the heart recovered and the pulse slowed; but the capillary reflux was still slow, and the blood pressure rose above normal, so that the patient passed into a condition of stupor.

The thyroid extract cleared the blood of uric acid, and doubtless with the rise of temperature quickened the capillary reflux; the blood pressure became normal (for we had then a fairly strong heart and a normal capillary circulation for the first time together), and the pulse quickened in accordance with Marey's law.

But normal capillary circulation with normal heart and blood pressure means normal functioning of the cerebral cortex, and normal mental condition, while low blood pressure from heart failure with obstructed capillaries means defective function of the cortex with excitement or mania; and high blood pressure with obstructed capillaries means stasis and hyperæmia (with or without some thrombosis and œdema), again accompanied by defective cortical function and stupor as its sign.

I could reproduce these conditions in any similar case, as the capillary reflux and blood pressure observed together would tell me the exact condition and what required to be done.

Cortical anæmia from heart failure before obstructed capillaries means delirium; cortical hyperæmia with possible stasis, thrombosis and œdema means stupor or coma.

Conditions of hysteria and excitement in women are but the reaction of their relatively weak hearts to collæmia. When men have weak hearts they also become hysterical (see case in chap. xiii.).

Given collæmia and slow capillary reflux, if a woman's heart does not fail she will have headache or mental depression or both, because blood pressure will be high; but if her heart fails she will have subnormal blood pressure in spite of collæmia and slow

capillary reflux, and then will be excited, hysterical, delirious, even maniacal.

Epilepsy holds an intermediate position, for the convulsion of epilepsy may be due to heart failure, but in the above case blood pressure was high at the time the heart failed, and it failed or stopped suddenly, being overpowered by the high blood pressure. In hysteria and excitement the heart fails for other reasons, so that blood pressure is not raised, but subnormal. It is clear from this pathology that we may get all gradations from one to the other, from epilepsy with high blood pressure up to the moment of heart failure, through hystero-epilepsy to hysteria and mania, where with cardiac failure the blood pressure is low; but in all cases the estimation of the capillary reflux and blood pressure will reveal the exact condition, and increased pulse rate is a constant sign of heart failure, *e.g.*, C.R., 7; P., 90—100; B.P., 120. It should have been 140 in relation to above C.R. if heart was strong. Roughly C.R. $\times$ 20 = corresponding B.P.

The one thing common to all cases is collæmia and slow capillary reflux, and the conditions then fall into two groups according as the heart fails, or does not fail.

In the heart failure group:—Excitement; hysteria; mania; syncope; epilepsy (with sudden heart failure).

In the strong heart group:—Headache; mental depression; melancholia (suicide); epilepsy (with high blood pressure); cerebral hæmorrhage.

This explains why women suffer from excitement after a shock and from Raynaud's disease, or girls from chorea, and why depression, suicide and cerebral hæmorrhage are less frequent than with men.

Collæmia, being the common factor, must be prevented, but in cases of hysteria and excitement when blood pressure is low in spite of capillary reflux being slow, measures must be adopted to strengthen the heart muscle as well.

Tabes dorsalis is another disease of which the exact causation does not yet seem clear, but it is generally considered to be a degeneration of nerve structure rather than an irritation or inflammation, and some observers are looking to the circulatory system for an explanation.

My attention was directed to the possible relation of tabes to the circulation some twelve or fourteen years ago, by a case in which tabes dorsalis occurred with signs of aortic regurgitation, and I used to ask what was the possible connection between locomotor ataxia and aortic regurgitation.

The answer in my mind was high blood pressure, for high blood pressure is, I believe, by no means uncommon in locomotor ataxia, and may be a cause of aortic regurgitation. I have certainly seen some very high blood pressure in cases of tabes, but experience does not enable me to say whether this is a constant concomitant.

Some of the conditions which tabes follows are not without suggestion; thus it may succeed any fever or acute rheumatism or pneumonia, and the relation of such to post-febrile collæmia and its effect on the circulation need not be repeated: or it may follow over-fatigue or exposure to cold or damp, and last, but not least, syphilis is the very disease which we might expect would intensify the vascular effects of uric acid collæmia, for obviously any degeneration of vascular tissues would increase the evil effects of obstructive collæmia, and we shall see in chapter xi. that syphilis has probably a similar effect in Raynaud's disease.

A fact of great interest has been pointed out by Dr. H. Oppenheim, of Berlin, and others (see *Berlin. klin. Wochensch.*, 1884, p. 603), namely, that megrim is a frequent feature in the previous history of cases of tabes, and if tabes is a result of high blood pressure or defective circulation, we have here as frequent antecedent a condition certainly associated with collæmic circulation, the uric acid headache itself. He found the history of such headache in 12 out of 85 cases of tabes, 10 of the 12 being females. Migraine is generally present for many years, but often increases in frequency and severity before the onset of the tabes. He considers that migraine is far too frequently met with in the history of tabes to be passed over as a mere accident, and that where migraine is present with increasing severity, an outlook should be kept for the early signs of tabes.

Dr. W. Sander in the same journal (*Berlin. klin. Wochensch.*, 1876, p. 289) makes a very similar remark as to the relationship between migraine and "dementia paralytica", or "paralytischen Geistesstörungen," which is, I take it, the disease I shall mention further on—general paralysis of the insane.

Here, again, migraine has been noted as an antecedent in $\frac{1}{10}$ or $\frac{1}{12}$ of all cases, but (unlike the tabes cases) the attacks may cease before the more serious mental disease comes on.

Apart from clearing the blood of uric acid by diet or drugs, there is only one reason I know of why migraine attacks should cease, and that is heart failure; the obstruction to the capillary circulation continues, but the pain ceases because the heart has no longer power to keep up the pressure.

Under these conditions it seems certain that degeneration of delicate nerve structures, such as those of the cortex of the brain, must ensue, and I doubt not that in the observation of Dr. W. Sander we have a key to the causation of general paralysis, namely, defective nutrition and consequent degeneration of delicate nerve structures, because the blood supply is hindered both by blocked capillaries in front and failing heart power behind.

I have several times had cases of so-called "softening of the brain," and have found exactly these conditions, namely, heart failure in people who for years had had high blood pressure and capillaries obstructed by collæmia. In such cases I have done more or less decided good by freeing the capillaries from collæmia and strengthening the heart, and if the pulse rate becomes normal, B.P. may resume its ordinary relation to C.R.

To strengthen the heart without freeing the capillaries would have brought back the migraine in the cases observed by Dr. Sander.

Allowing that it is only in a small number of these cases headache is an antecedent, we must remember that by no means everyone with high blood pressure suffers from headache. What I find suggestive is that in so many cases a headache which was undoubted evidence of high blood pressure was found, and probably in many more there was antecedent high blood pressure, though it produced no headache.

Another indication is the insomnia which Dr. Sander ranks with migraine as a common antecedent. In my experience of migraine or mental depression with high blood pressure, some amount of insomnia is a constant symptom, and I have long regarded a uric-acid-free diet as a cure.

With tabes we must remember the anatomy and physiology of the cord circulation; that it is carried on through considerable lengths of small vessels, where peripheral obstruction and high blood pressure would probably have great effects in slowing the blood stream; and here we see, perhaps, a further link in the connection of tabes with aortic regurgitation, for such regurgitation might act very much like the heart failure in cerebral paralysis and greatly increase the circulation difficulties in certain portions of the cord.

Nor is the fact that degeneration in tabes is limited to certain definite tracts in the cord, a bar to such circulatory origin of degeneration, for in all such complex organs there must be parts in which the capillary circulation is carried on with greater difficulties than elsewhere, and those will consequently be the first to feel the stress of famine.

I have certainly seen cases in which paresis of the lower extremities appeared to be associated with slight heart failure in a circulation obstructed by collæmia, and in at least one the symptoms were markedly worse in the morning hours for reasons which will now be understood (see also Dr. Handson's case in chapter xiii.).

I suspect also that some cases of temporary loss of power in the legs from severe mental shock have a similar causation, for shock, as we know in chorea, Graves' disease, &c., is a cause of collæmia, and collæmia may soon produce heart failure, temporary or permanent.

It is of interest that general paralysis is not uncommonly associated with tabes, and that, as is the case with tabes, there is little to negative the possibility of its being essentially a degeneration of nervous tissues originating in circulation and vascular changes, such as stasis and thrombosis, as seen, for instance, in the retina in the high blood pressure conditions of migraine (see references on p. 212).

This pathology explains why this disease is so often the sad ending of men of great mental power, for it is precisely the most delicate cortical tissues with the finest meshwork of capillaries that will be most affected by the circulation failure and will most quickly degenerate.

The curve of annual incidence of this disease in Paris, as given by Mr. Havelock Ellis, has a maximum in May and June corresponding closely with the maxima of the curves of insanity and suicide, and the large uric acid excretion of early summer, to which I have already referred (p. 152).

For a record of the suggestion that highly nitrogenous foods (for which I should read uric-acid-containing foods) have an influence on the causation of general paralysis quite apart from syphilis, see Dr. W. Ford Robertson in the *British Medical Journal*, 1901, vol. i., p. 1602.

I give these facts for what they are worth and to emphasise the suggestion I have made that in all functional and organic diseases of nerves and nerve centres of obscure origin, capillary reflux and blood pressure should be investigated, and when abnormal carefully treated with a view to reproduce normal conditions and test the effects of the circulation changes on the disease.

So much for depression or fatigue of mind, but I believe fatigue of body has a similar if not identical causation. If bodily strength and power of endurance are increased by drugs like opium and cocaine, which produce a free circulation and metabolism in the

nerve centres and muscles, then obviously conditions which hinder the circulation and diminish the metabolism will produce fatigue of body as well as depression of mind.

I pointed out a good many years ago* the fact that a fall of uric acid excretion brought about by the administration of an acid was almost always accompanied by a rise in the excretion of urea.

Since that time I have ascertained that uric acid taken by mouth is not converted into urea, but is in due time excreted as uric acid in the urine † (see figs. 24 to 30).

Also that while a marked fall in uric acid is commonly accompanied by a rise of urea, a marked rise of uric acid is also commonly accompanied by a fall of urea.

It was only, however, in working at the physiology and pathology of fatigue that I appreciated something of the real bearing of my observations.

The effect of exercise is to lower the acidity of the urine owing to the increased excretion of acids by the skin in perspiration; the fall of acidity, or more accurately the increased alkalinity of the blood, allows the passage of an excess of uric acid, and this is accompanied by a fall of urea and the presence of more or less marked fatigue.

Here, then, is the physiology of fatigue, depressed and deficient circulation in the muscle and nerve tissues owing to the excess of uric acid in the blood; and this explains the disinclination for bodily and mental exertion which accompanies the uric acid headache, or mental depression due to the same cause.

We can understand that fatigue, with its raised blood pressure and slow capillary reflux, is the physiological epitome of all defective combustion, and the fall of the urea is the sign of the defective metabolism of albumens.

Prolong this collæmia and defective combustion over weeks instead of hours and let it affect especially the albumens, and you get not only a fall of urea, but an excretion of uncombusted albumen—albuminuria or Bright's disease; let it affect the carbohydrates and you have glycosuria or diabetes, or let it affect the fats and obesity follows, very often combined more or less with the other two.

In studying fatigue we survey the pathology of all these failures of combustion in epitome. The high blood pressure and slow capil-

* *Journal of Physiology*, vol. viii., p. 215.

† *Ibid.*, vol. xv., p. 167.

lary reflux common to them all are signs of what is going wrong in the tissue metabolism, and the tissue metabolism is upset because the capillary circulation is defective.

But if fatigue is thus due to the presence of excess of uric acid in the blood, and if opium and cocaine can for a time abolish fatigue by keeping the blood clear, it follows that fatigue will be absent or very slight so long as uric acid is absent from the blood, no matter what method is adopted for bringing about this result.

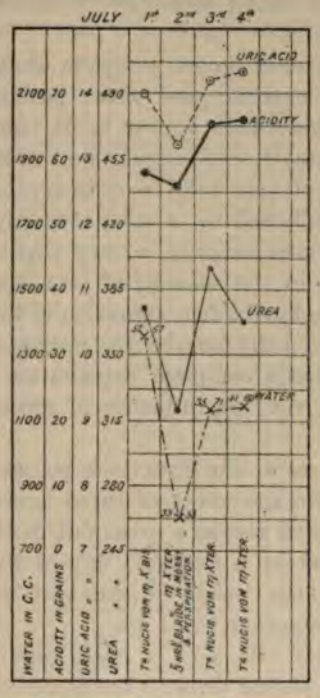

FIG 46.—EFFECTS OF EXERCISE ON THE EXCRETION OF URIC ACID AND UREA (MORNING).

And as there are many ways of keeping the blood clear of uric acid, it follows that there are also many of preventing fatigue besides the use of opium, cocaine, or other retentive drugs.

Opium and cocaine keep the blood clear of uric acid by raising the acidity; they thus counteract the effects of exercise and prevent the blood becoming a good solvent of uric acid as its result.

But there is another way of keeping the blood clear under these conditions, namely, by previously clearing out with solvents the uric acid available.

The most powerful solvent and excretant of uric acid is salicylic acid or one of its salts, and if these are given for four to five days before the exercise is taken, so as to sweep out all uric acid available for solution in the blood, and if the drug is left off on the day of exercise, some remarkable results are obtained.

First there is a great fall in the excretion of uric acid, which always occurs after salicylates have been taken for a few days and left off, so that there is no uric acid to come through the blood as the result of the rising alkalinity of exercise and perspiration (see fig. 8).

And with this there is almost complete absence of fatigue (even with the severest exercise and most profuse perspiration) and muscle power and endurance appear to be increased at least 50 per cent. Further, there is this remarkable result, that, whereas with the plus excretion of uric acid in ordinary exercise there goes a great fall of urea followed by a rise next day, there is either an immediate rise of urea or only a very slight fall in the case of exercise undertaken in the absence of uric acid from the blood.

In these facts we have a demonstration of the enormous influence exerted by uric acid on the metabolism, nutrition and function of the whole body, and also a complete explanation of a much-disputed point in physiology, viz., the influence of exercise on the excretion of urea.

I give a few figures to illustrate these points.

In fig. 46 is shown the effect of three hours of bicycle work in the a.m. hours, with its result, a great fall in the excretion of urea, viz., 57 grs., followed by a rise next day of 78 grs. Take the fall from the rise and the result of the two days is an increased excretion of urea amounting to 21 grs.

Note further that uric acid is fairly high above urea, so that probably 4 grs. of it passed through the blood on the day of exercise.

In fig. 47 is shown, in contrast with the above, the effects of three hours bicycle exercise in the p.m. hours of the day; the amount of work done in the two cases is as nearly as possible identical.

Here we see a fall of only 36 grs. followed by a rise of 60 grs. next day, and subtracting the former from the latter we get a rise of 24 grs. of urea as the result of the two days, so that while the amount of exertion was as nearly as possible the same in both figures, the resulting increased excretion of urea was the same all but 3 grs. The point which these figures illustrate is that for the same amount of exercise the fall of urea that results is

greater when the exercise is taken in the a.m. hours than when it is taken in the p.m. hours, and that this is due to the fact that there is generally more uric acid available for solution in the blood in the a.m. than in the p.m hours (see figs. 1, 2, and 3); for we shall see that the fall of urea that accompanies exercise and fatigue is entirely dependent on the amount of uric acid in the blood, and that the amount of fatigue produced by any given exercise varies absolutely with the fall of urea, and is therefore dependent on the amount of uric acid in the blood.

This is no chance result of a single experiment, for I have

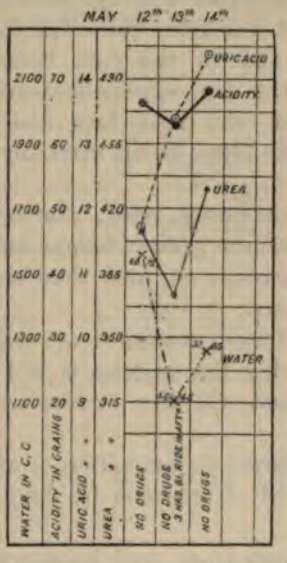

FIG. 47.—EFFECTS OF EXERCISE ON THE EXCRETION OF URIC ACID AND UREA (AFTERNOON).

worked at these points for several years, and it was the remarkable fall of urea that always accompanies exercise in the a.m. hours that first drew my attention. It must be understood that exercise always produces a rise in the excretion of urea. The quantity of uric acid in the blood determines whether that rise shall come at once with little fatigue, or not till next day with more decided fatigue; and it was through overlooking this relation to uric acid that the effect of exercise on the excretion of urea was misunderstood.

I remark in this connection that Dr. Vaughan Harley has pointed out * that less muscular work can be done at 9 a.m. than

* *Lancet*, 1884, vol. i., p. 1199.

at 11 a.m., and that muscle power rises from 9 to 11 a.m., and that there is also a notable fall in muscle power at 4 p.m. And it is a remarkable fact that there is generally more uric acid passing through the blood at 9 a.m. than at 11 a.m., and about 4 p.m. there is generally also a temporary rise in the excretion of uric acid (afternoon alkaline tide, see fig 1).

I think almost every one must have made the clinical observation that children are often dull and heavy, and disinclined for mental and bodily exertion in the a.m. hours; while they are lively and can hardly be restrained in the p.m. hours.

A priori one would expect that the facts would be exactly the reverse, for in the a.m. hours the child has just been refreshed by a long night's rest, and in the p.m. hours it has borne the burden and heat of the day. There is a great difference in this respect between those who take flesh and tea and those who abstain from them, the latter being markedly bright and fresh in the morning hours.

In physiological conditions, then, exercise undertaken in the a.m. hours generally causes greater fatigue and a more marked and decided fall in the excretion of urea than similar exercise undertaken in the p.m. hours.

We shall now see that if measures are taken to keep the blood clear of uric acid during the exercise it will be accompanied by little or no fatigue, and will also produce little or no fall in the excretion of urea.

I have already referred to the action of opium, and to the fact that it clears the blood of uric acid by diminishing the alkalinity of the blood.

This action of opium is so well known that I wished to give a figure showing its effects on the excretion of urea and uric acid in myself during exercise, but I was met by this difficulty.

My diet (1890) is one in which milk is almost the only animal food, and I further consume a considerable quantity of fruit. The result is that I have a large introduction of alkaline bases and but a small introduction of acids and acid salts, such as the sulphur and phosphorus and the phosphates and sulphates of animal tissue. Therefore the acidity of my urine is much lower than that of those who eat ordinary diet, and the alkalinity of my blood probably much greater.

Hence I found that opium (in such doses as I cared to take), had comparatively little effect on the acidity of my urine, and as it thus affected the alkalinity of the blood but slightly, it failed to

clear the blood of uric acid, and also failed to prevent fatigue and a fall of urea when exercise was taken.

It may be objected that the rise of acidity in fig. 15 is well marked, but this was obtained some years ago when my diet still contained some flesh, fish or egg.

I therefore selected a drug which cleared the blood of uric acid independently of acidity; viz., mercury, though other metals, as copper, zinc, silver, would have done equally well, and I have no doubt that the action of these metals in forming insoluble compounds with uric acid accounts for their so-called tonic effects. The action of all these metals can now be easily demonstrated by their effects on the granules of uric acid in the blood, the capillary reflux, the

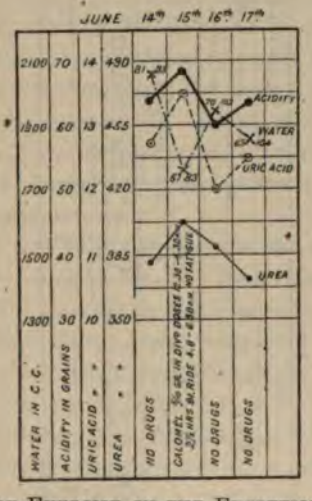

FIG. 48.—EFFECTS OF EXERCISE ON THE EXCRETION OF URIC ACID AND UREA AFTER CALOMEL.

blood pressure, and on the temperature which the circulation controls.

I have pointed out that the urates of mercury are insoluble, and fig. 48 shows its effect in the form of calomel on the excretion of urea under exercise. We see that there is an immediate rise of urea to the extent of 23 grs., followed by a fall next day; and with this rise of urea there was not only absence of fatigue but a feeling of increased muscle power and endurance.

But there are other ways of keeping the blood clear of uric acid besides giving mercury, opium, or other drugs which directly or indirectly diminish the solvent powers of the blood for uric acid.

And perhaps the best way is to take a course of salicylate as

above mentioned, and fig. 49 shows the effect of some exercise taken the day after a dose of salicylate which had caused a very large excretion of uric acid; on the day of exercise the uric acid fell greatly and was slightly below urea, and with this there was an immediate rise of urea to the extent of about 19 grs., followed by a fall next day.

I have made many similar experiments, but shall only mention my results in one more.

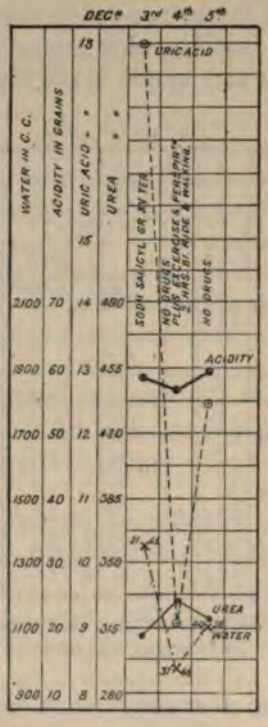

FIG. 49.—EFFECTS OF EXERCISE ON THE EXCRETION OF URIC ACID AND UREA AFTER A COURSE OF SALICYLATES.

On the 10th of June, no drugs having been taken for several days, I rode 35 miles on a bicycle, the exercise beginning about 11 a.m. and ending about 5 p.m., with a considerable rest in the early part of the afternoon. This produced a fall of urea = to 27 grs., followed by a rise of 52 grs. next day, and the same rise was maintained on the following day, though this was partly accounted for by further exercise.

On the 24th of June, after a four days' course of salicylate of

soda (the drug having been left off), I rode at about the same hours of the day 45 miles on a bicycle.

The daily curves show uric acid decidedly below urea and a fall of urea equal to 18 grs. followed by a rise of 23 grs. next day and 70 grs. the day after.

My notes show, however, that on the day this exercise was taken my food was unfortunately deficient for at least one meal, and but for this I think that there might have been no fall of urea on the day of exercise, and a greater rise on the day that followed it. As it is, however, the difference between a fall of 27 grs. for 35 miles and a fall of 18 grs. for 45 miles, is sufficiently marked, and on the 45 mile day there was little or no fatigue, in spite of severe exercise and perspiration, till supplies of food began to run short.

I have been told by Dr. W. Kidd, of Blackheath, that he has had somewhat similar experience with salicylates, in that having taken these drugs for several days for uric acid headaches he was surprised to find that he was able, though quite out of training, to ride 45 miles on a bicycle with as much or more ease than he could previously ride 20; and many other observers and athletes have now corroborated these experiences.

There is another way in which the amount of uric acid available for solution in the blood can be diminished, and that is by diminishing the daily introduction. (See *Journal of Physiology*, vol. xv., and *Brit. Med. Jour.*, December, 1894.) This is an experiment constantly being performed for us by others; I refer to vegetarianism. In the second edition, p. 163, I have referred to the fact that in a long distance walk which is mentioned in the *Lancet* (1893, vol. i., p. 1396), the winners out of a large number of competitors were vegetarians. I have also quoted in "Diet and Food" (fourth edition, p. 99), another remarkable instance, of which the heading in the *Daily News* was, "Meat-eaters Walked Off Their Legs," and I believe there need be no difficulty in repeating this result, and it has now been done year after year. Those on a uric-acid-free diet can always walk meat-eaters and tea-drinkers off their legs, for the reasons I am here giving in detail (see also "Muscle, Brain, and Diet," by E. H. Miles: Swan, Sonnenschein and Co., London, 1900; also a paper of mine in the *Edinburgh Medical Journal*, December, 1907).

It is precisely in the long distance that absence or relative absence of uric acid tells; the meat-eater will do very well at first; the relatively low alkalinity of his blood suffices to keep it pretty free from uric acid for a time in spite of the exercise; but

when alkalinity rises decidedly, inevitable collæmia results, and he is then quickly outpaced by the vegetarian competitor.

Persons accustomed to the stimulation of animal flesh have mistaken this stimulation for strength, and have evidently the greatest difficulty in believing that anyone can possibly be fit for exertion on any other diet. Thus a sedentary patient of mine had a beef-eating friend who prided himself on his walking, and, to escape further chaff on diet matters, my patient accepted his challenge for a good walk. The result was that my patient walked him off his feet with comparative ease, and when some 20 miles had been covered the beef-eater acknowledged that he was tired and did not care to go further.

Professor Windle, of Birmingham, told me when he had been on diet about twelve months, that 75 miles on a bicycle, half of it against a strong head-wind, did not suffice to produce fatigue, and that, in fact, in his experience just as in my own, the old severe fatigue compelling an immediate rest at all costs was now unknown.

I find that exposure to heat during exercise has now comparatively little effect; instead of producing exhaustion and a speedy breakdown, it rather improves the pace and does not interfere with endurance. Formerly it quickly produced such extensive and severe collæmia that further effort became impossible, but now there is no material for such collæmia, and any little uric acid left has its solubility improved by the heat, so that collæmia is prevented instead of being produced.

Under these conditions exercise in not now accompanied by a great fall in the excretion of urea, because these waste products are at once removed from the muscles so that they can continue the production of force almost indefinitely, if albumens are supplied.

Further instances were prominent in the daily papers during the war between Turkey and Greece. There were many reports from the surgeons of the wonderful vitality of the Turks, of their powers of endurance without food, of their fighting and marching after the receipt of serious wounds, and of the way in which they recover and their wounds heal.

Here the free capillary circulation so essential for the repair of wounds, which English surgeons must produce with opium, is possessed by these Turks not only for a few hours while under the influence of a drug, but from birth to old age. For similar records in the medical papers see, among others, the *British Medical Journal*, 1897, vol. i., p. 1219.

I have no doubt that this magnificent nutrition and power of

endurance, this resistance to depression and shock after injury is due to the absence of collæmia which a uric-acid-free diet produces. It can be produced also by opium or mercury without change of diet, and the only factor common to all is absence of uric acid.

If a flesh-eater goes two hours longer than usual without food he gets collæmia; hence the saying, "a hungry man is an angry man"; but in the absence of collæmia much work can be done fasting.

Similar demonstrations of vitality and power of endurance have been given over and over again in the history of the world, and these facts are now acknowledged both in Europe and America, an increase of endurance of 100 per cent. and more being often recorded. See paper by Prof. P. Fauvel in *Monographies Cliniques*, December, 1907.

The advantages of the uric-acid-free diet are many, for in addition to comparative absence of fatigue during exercise there will be no succeeding stiffness or rheumatism—which provides another instance of the relationship between the latter and uric acid. On ordinary diet I never got hot in summer with subsequent exposure to cold or draught without stiff neck, lumbago, or some such trouble. This is now never the case, and Professor Windle's experience corroborates mine.

It will probably be asked why do horses suffer from rheumatism, not only arthritis, but endocarditis and pericarditis? They are vegetarians and ought, some may think, to be free from these troubles?

The answer to this is not difficult after a study of fig. 75, where it appears that one of the foods given to horses (the pulses—peas, beans, and lentils) contains even more uric acid or xanthin than animal flesh.

Horses also live in an artificial state, and some of their foods are highly nitrogenous (beans and cereals). These are given without any real reference to the nitrogen required for body weight or work, and there is little doubt that if allowed to satiate themselves on such strong foods they often get too much albumen, and will consequently form and retain too much uric acid.

Not only so; but when fed on dry foods and deprived of fresh vegetable substances they may suffer from a relative deficiency of alkaline salts in the blood, and thus have increased retention.

It is clear from the record given further on that horses suffer from fatigue and sleeplessness, and that, as in men, these symptoms can be relieved by opium.

Briefly they have uric acid collæmia and its results, and when exposed to cold and wet after fatigue they also get a precipitation of this urate upon their joints and other fibrous tissues, and vegetarians, who take similar foods containing xanthin, have no immunity from rheumatism or fatigue. Hence the vegetarian natives of India suffer from gout, rheumatism and stone, and statistics show that those suffer most who live largely on the pulses and other xanthin containing foods.

I may say in further explanation of these statements that absolute freedom from collæmia (that is from the presence of sufficient uric acid in the blood to produce abnormal fluctuations in capillary reflux and blood pressure) can only be obtained by non-introduction of uric acid or xanthin in the food, combined with such complete solubility of all the uric acid in the body that day by day there shall be excreted from it every grain formed.

If excretion falls short of formation by only half a grain a day, in twelve days there are six grains of uric acid available, and this will suffice to produce collæmia with any of its minor evil effects on circulation and nutrition for at least some hours.

To mention only the main points, the alkalimity of the blood is diminished by :—

(1) High urea ;
(2) Acids in food ;
(3) Exposure to cold and deficient exercise ;

and conversely it is increased by :—

(1) Low urea ;
(2) Alkalies in food.
(3) Warmth and exercise causing perspiration.

We must remember that every molecule of albumen metabolised in the body forms its nitrogen into urea and its sulphur and phosphorus into acid substances, hence acidity and urea rise and fall together.

The effects of acids and alkalies in the food are obvious, and cold and deficient exercise diminish the excretion of acids from the skin in perspiration and also directly precipitate collæmia on surfaces and extremities, for cold is itself a precipitant of uric acid and always acts as such except in the presence of salicylates.

The first requisite for this freedom then is moderate urea, and for sedentary people in cold weather this must not be more than 3 grains (9 grains of albumen) per pound of body weight per day, perhaps even a trifle less.

In warm weather (but still sedentary) a fraction over 3 grains a

pound may do, and in warm weather with plentiful exercise 3·5 grs. per pound per day will not suffice to produce retention, and in the young and active probably 4 grs. and more may be excreted with impunity under these conditions.

But if this quantity is taken in cold weather and when sedentary, there will be retention, and, now and then at intervals, some collæmia and its results.

This will be a slight matter compared with the severe collæmia of introduction with excess of albumens and a large supply of acids in food and drink (that is to say, with the introduction and retention of ordinary diet), at worst it may only amount to a little weariness in the head and a slight disinclination for exertion.

Thus to obtain the greatest possible freedom from collæmia while sedentary and in cold weather, we must keep urea moderate, we must avoid acids in food and drink, must eat potatoes, containing plentiful alkaline salts, and keep very warm. For even if the cold is not felt it will affect the acidity of the urine and the alkalinity of the blood.

I will add, as a practical rider, when any man feels a twinge in a joint, let him cut down albumens and acids and take extra potatoes, and he will soon be all right again.

Of course, if urea is too low nothing can be done. The standard must be observed. But with sedentary work less albumen is required, while with increased exercise it may be slightly increased with impunity. The above rules are a treatment of disease. Those who have never been diseased, and who live a natural, healthy, active life, can take the full quantities allowed by physiology, say from 9 to 10·5 grains per day for every pound of net body weight (muscle and bone, not fat).

But to return: these facts seem to demonstrate that fatigue is proportioned to the amount of uric acid available for solution in the blood at the time that any given muscular exertion is undertaken, and that the immediate effect of the exercise on the excretion of urea is similarly determined.

These results of mine correspond with those of Parkes, for he often found a diminution of urea during exercise followed subsequently by a slight rise; and they serve to explain also the conflicting evidence and contradictory results of other observers.

My results bear also in a most important manner on the explanation to be given of the results obtained by Fick and Wislicenus in the celebrated experiment in which they performed a certain amount of work on a non-nitrogenous diet and estimated the nitrogen excreted,

with the result that the excreted nitrogen fell short of the amount required to account for the work performed.

From this experiment it has been concluded that their muscular energy had other sources besides proteid metabolism, and this may still be the correct conclusion, though the results I am now bringing forward must, I think, be regarded as modifying it considerably.

In the first place, my experiments show that exercise always produces sooner or later an increase in the excretion of urea, and I am certain of this fact, as I have been watching it for years in my daily work at the excretion of uric acid and urea, and have hundreds of curves to prove it. I am also in complete accord with the results obtained by North* in his elaborate and careful experiments; he showed that in times of rest there was a storage of nitrogen in the body, and that after exercise there was an increased excretion of a roughly corresponding amount.

My results further show that the time at which this increase of urea is excreted depends on the amount of uric acid present in the blood. Clear the blood of uric acid, by no matter what means, the exercise will be accompanied by an immediate rise of urea; flood the blood with uric acid, and there will be an immediate fall of urea, followed by a rise next day.

Clearly, then, the differences and contradictions between the results of previous experimenters were due to ignorance of this fact, which has a special and important bearing on the experiments of Fick and Wislicenus, for they did their work on a non-nitrogenous diet.

One effect of placing themselves on such a diet would be a fall in the acidity of the urine and a corresponding increase in the alkalinity of the blood; and the natural and only possible result of this would be (as they had exercised no care to clear out uric acid beforehand) that their blood would be forthwith flooded with a more or less large amount of uric acid from the stores in their bodies; the result of this being (as we have seen above) that muscular exercise would be accompanied by a fall in the excretion of urea.

No doubt next day, as in my experiments, there would be a rise that more than compensated for the fall; but these experimenters estimated the nitrogen of twelve hours before labour, three hours during labour, and six hours' rest after labour, and

* *Proceedings of the Royal Society*, 1885, p. 501.

drew their conclusions from these. This period would not be nearly long enough to include the rise that followed the fall, hence the nitrogen they obtained was far short of the amount really excreted as the result of the exercise taken, and their results are to this extent fallacious.

Though this argument applies to their experiments as a whole, it is interesting to note that they did get an immediate increase of the excreted nitrogen at the time of the exercise, thus:—

*Nitrogen excreted in grms. per hour.	Fick.	Wislicenus.
In 12 hrs. before the labour ...	·575 gr. per hr.	·556 gr. per hr.
In 3 „ labour ...	...1·103 „ „ „	1·043 „ „ „
In 6 „ rest after labour ...	·405 „ „ „	·403 „ „ „

But this no doubt corresponded absolutely with the excretion of uric acid and the amount passing through the blood, for though they took no nitrogen during the experiment, the nitrogen they had previously taken served (as shown by North) to keep them going and prevent any great increase of the alkalinity of the blood until the exercise had been continued for some time. Towards the end of exercise, and still more in the rest afterwards, there would be a great rise in the alkalinity of the blood, increased by the absence of nitrogenous food, and it would be flooded with a correspondingly large amount of uric acid.

The result of this would be what the above figures show us: a great fall in the excretion of nitrogen in the hours that follow the labour, for during the hours of labour it was upwards of 1 gramme per hour for each of the experimenters, but in the rest which followed it fell to less than half a gramme.

If the hours of labour had been examined hour by hour I have no doubt that the larger excretion of nitrogen would have been found in the first hour and a half or two hours, and after that there would be a considerable fall, and if uric acid and urea had been separately estimated uric acid would have been found below urea (in the relation 1—35) at the beginning of the labour, but far above it towards the end and in the rest which followed (see also previous remarks about vegetarians and meat-eaters).

The amount of uric acid in the blood not only controls the excretion of urea under exercise, but under all conditions from hour to hour and day to day, and practically every rise of uric acid is accompanied by a fall of urea, and every fall of uric acid by a rise of urea.

* From figures given in Prof. Foster's "Text-book of Physiology," 1877, p. 325.

In verifying these statements, however, those who come to the subject *de novo* must remember certain simple propositions, viz., that the rise or fall of uric acid must be sufficiently decided to overcome other concomitant fluctuations in a reverse direction; for instance, it would require uric acid to be very high indeed to overcome the rise of urea that generally follows the day after exercise, but in pathology uric acid may be high enough even to do this if its rise is in part the result of a complete upset of gastro-intestinal digestion. But if uric acid has been for some hours above urea and is brought down below it suddenly with any drug, the probability is that there will be a fairly marked rise of urea corresponding to its fall; while, if uric acid has been close to urea for some hours before the drug is given to bring it lower, the rise of urea may be too small to show in the curves.

And it was, as I have pointed out, the rise of urea following the ingestion of uric acid that was thought by Sir A. Garrod and other observers to show that the uric acid given had been converted into urea; whereas we now know that any acid or metal clearing the blood of uric acid will produce a similar rise of urea, and yet these substances introduce no fresh nitrogen into the body and are incapable of conversion into urea.

We also know that uric acid taken by the mouth acts as an acid, and for a time clears the blood of uric acid, and so causes a rise in the excretion of urea; but *the uric acid taken* has not been converted, but merely retained in the liver waiting for a solvent, and will pass out in the urine a few days later, and increase the ordinary excretion in proportion to the amount swallowed (see figs. 24 to 30; also *Journal of Physiology*, vol. xv., pp. 167 and 170; and *British Medical Journal*, December, 1894).

If, then, uric acid in the blood controls, as above pointed out, from hour to hour, day to day, during and after exercise, the excretion of urea, we may consider how it produces such effects.

I have for years been pointing out that uric acid in the blood controls the circulation, and that its excess is at all times accompanied by high blood pressure and deficient capillary circulation, the latter being the cause of the former.

I have further said that the best proof of this is to be seen in the hourly and daily excretion of water by the kidney varying inversely with the uric acid also excreted from the kidney.

I believe there can be no explanation of this fact save that I have given; that the uric acid directly or indirectly obstructs the flow of blood through the capillaries of the kidney and thus hinders the passage of water out of the blood into the urine.

But investigators must remember certain cautions; first, that when there is no excess of water in the blood, freeing the capillaries by clearing the blood of uric acid will not produce a diuresis; and second, that when the blood is cleared of uric acid, even for a short time, there may be so great a diuresis that if care is not taken to separate excretions accurately the urine of several hours may seem to be profuse, though the uric acid during the major part of the time is not at all scanty. Separate accurately from hour to hour (or if necessary from half hour to half hour), and you will see that the great diuresis corresponded with low uric acid, and there are plenty of figures which show this (see fig. 3 and my remarks about it).

Apart from such sources of mistake, uric acid and urinary water vary inversely in everyone from day to day or hour to hour, and every drug that clears the blood of uric acid produces a diuresis if there is any water to be run off, the action of all the best-known diuretics being a simple illustration, for they all diminish the excretion of uric acid.

Only in those whose bodies are nearly free from uric acid is a free flow of water possible along with an excretion of uric acid say 1 to 25 under alkali, *i.e.*, with low acidity of the urine.

In such circumstances the total excretion of uric acid in the day is small, the amount available in the body is small, and the alkali is present in such quantity that it holds all the uric acid, in or available for the blood, in good solution. Hence the capillaries are little obstructed by collæmia and, given sufficient available water, a diuresis takes place.

Give the same amount of alkali in food or drugs to an ordinarily fed man, and so much uric acid will be brought into the blood stream that the alkali will be unable to hold it all in satisfactory solution, and the capillaries will be blocked with colloid. The urine will be scanty, and only as the supplies of available uric acid diminish will there be a solution of the collæmia and a diuresis.

The fact that a diuresis may occur with low acidity of urine and an excretion of uric acid to urea of 1 to 25, shows that when alkali is present in a certain proportion to the uric acid or urates in the blood stream, the granules may be dissolved or become so small that they no longer obstruct the capillaries. It shows also that collæmia can be dissolved by alkali, but that this is only possible where the quantities of available uric acid are small; that in the body, just as under the microscope, the more alkali the smaller the urate granules, and that when small they hardly obstruct the capil-

laries at all, and do not prevent diuresis or cause any marked rise of blood pressure; that in some conditions collæmia is not co-extensive with uricacidæmia, that there may be a slight excess of uric acid in the blood without any notable collæmic obstruction of capillaries; but this is a physiological condition, and in all pathological conditions collæmia is co-extensive with uricacidæmia, and synonymous with it as used in this volume.

We have also in fig. 5 independent evidence that exercise increases the amount of uric acid in the blood, for it increases the distance between the mouth and rectal temperatures; it also appears to do this to a greater extent in the alkaline tide hours than in the evening hours, the exact parallel of its effects on excretion of urea and fatigue.

If, then, it be granted that uric acid in excess in the blood does obstruct the circulation in the capillaries of the whole body, it is easy to see how it produces fatigue and the fall of urea which accompanies muscular exercise, except when the blood is specially cleared of it.

For obviously deficient circulation must mean deficient metabolism in all organs and tissues, and deficient removal of waste products, hence excess of uric acid in the blood diminishes the excretion of urea during exercise and produces fatigue. It affects the muscular and nervous tissues at the same time, producing fatigue of body and dulness and depression of mind.

The effect of uric acid on tissue metabolism is to produce slow and deficient combustion. It may be compared to a wet blanket on the kitchen fire with all the flues shut. The wet blanket corresponds to the collæmic obstruction of the capillaries, with the products of previous metabolism left to clog the tissues, so long as circulation is defective; and the removal of the wet blanket is the cause of the rise in urea which accompanies the next fall in uric acid. Obviously this rise in urea is proportioned not necessarily to the fall of uric acid, but to the amount of interference with metabolism that had previously taken place in the tissues. Hence the rise of urea that follows the clearing up of collæmia is generally only a matter of 10—15 or 20 grs. in physiological conditions, but in Bright's disease, where the failure in metabolism and removal of waste products has been of longer duration and greater extent, the rise may amount to 100 grs. or more (see chapter xiii.).

I conclude that the effect of exercise is to increase the formation of urea, and that, if there is a free circulation through the tissues owing to comparative absence of uric acid from the blood, this

urea will pass almost at once into the urine and be excreted. With this will go comparatively little fatigue. If there is a quantity of uric acid in the body or food, so that the rise of the blood's alkalinity (which the exercise and perspiration produce) can dissolve a large amount and bring it into circulation, there will be deficient circulation in all the tissues with a fall in the excretion of urea and great fatigue, because the tissues are clogged with waste products, as well as insufficiently supplied with fresh albumins. Continued exertion may then be almost impossible and, if persevered with, may lead to syncope and more serious troubles.

Further, as we have seen, it is possible by controlling the uric acid to control the result.

Professor M. Foster, writing on the physiology of weariness in 1893,* attributes it to the presence of poison in the blood. I believe my researches demonstrate that the poison is uric acid. I may point out that these facts explain the observed relations between fatigue and weather changes, *i.e.*, that fatigue is greater in warm and less in cold weather. Obviously the warmer the weather the greater the perspiration any given exertion produces, and the greater the perspiration the greater the rise in the alkalinity of the blood, and the sooner (other things equal) will it contain excess of uric acid.

On the other hand, a cold wind or a cold frosty day will tend to diminish perspiration, and hence will reduce and delay the increase in the alkalinity of the blood; under these conditions much more exercise can be taken without fatigue, just as with mercury, opium, &c., and for the same reasons; for the muscles are kept longer free from the deficient circulation, nutrition, and metabolism which collæmia produces.

The argument that has been here applied to the production of energy by muscles, holds also probably for the production of heat by these and other tissues. That is to say, when the blood is clear of uric acid, there will be increased production of energy and heat throughout the tissues. External cold will increase the production of heat, and external warmth will diminish its production, just as we have seen that they also increase and diminish the production of muscular energy, and in the action of uric acid on the vessels we have at once established a regulating mechanism that damps down the fires of life when they are not wanted, but allows them to burn brightly when an increased production of heat is required.

* *Lancet*, 1893, vol. i., p. 1457.

I give a case of slight fatigue (that of Weston, the pedestrian), the signs of which have been carefully recorded by the late Dr. Mahomed (*British Medical Journal*, March, 1876), with the object of showing that they are practically those of collæmia. It is recorded of March 10 and 11 that he lost weight and became sleepy, that his pulse tension "was now very considerably increased," and that there was a coincident fall of temperature. "His hands felt cold instead of glowing as heretofore; he complained of feeling chilly and required more bedclothes. The second sound of his heart was accentuated, and the first a little prolonged." These are the signs of collæmia, and no doubt they were accompanied by a fall in the excretion of urea, and were contemporaneous with and due to an excess of uric acid in the blood. They are the common symptoms of the uric acid headache, the causation of which has been discussed, and estimation of capillary reflux and blood pressure would tell the exact condition.

On March 12 the pulse tension had again become low; with this temperature rose and his extremities became warm. "After this he awoke much refreshed, and continued to walk well and easily to the end of the match. This probably was coincident with the change in arterial tension."

I quite agree as to these changes of condition being coincident with the change in arterial tension, but they were more than that, they were absolutely due to the same cause. When uric acid was cleared out of the blood the capillaries were freed, the nutrition of the muscles and nerve centres improved, the surface temperature rose, and the signs of fatigue vanished.

One of Weston's competitors suffered more severely from the same symptoms, having probably a more severe and prolonged collæmia, and had to give up the match.

Among other symptoms of this condition specially mentioned are a feeling of weight and discomfort in the præcordia, cough with increased secretion of bronchial mucus (see chapter ix.) and albuminuria. The pulse then requires much pressure to develop it "on account of the fulness of the artery," in other words, high blood pressure.

The man who first gets slow capillary reflux and high blood pressure is the man who will first break down, and those who are most affected by exercise and heat have most collæmia and most available uric acid.

Reduplication of the first sound of the heart is such a common occurrence in all high blood pressure conditions that I was much

interested in an article by Dr. A. G. Phear, *Lancet*, 1902, vol. ii., page 1537, in which he indicates that one of the more important factors in the production of the first sound is the vibration generated in the auriculo-ventricular valves in the course of the ventricular systole. If the valves are thrown into tension simultaneously the resulting sound is single, but if not the resulting sound is more or less doubled, and it appears evident that in conditions of high blood pressure there must often be a very different pressure in the two ventricles, and a corresponding difference in the amount of tension strain put on the valves of the right and left sides. Consequently there must of necessity be some difference in the time at which structures of the right and left side arrive at their greatest tension, for we know that where the pressure in the systemic circulation is great the corresponding systole is more prolonged; consequently in high blood pressure conditions it must take longer to get the mitral valve into full tension and a shorter time to get the tricuspid valve into this condition. Hence all rise of blood pressure will tend to produce some reduplication of the first sound, and this will be intensified and increased by anything causing weakness of the heart or debility of its muscles. This is exactly what we find, and marked reduplication of the first sound is a common sign of early heart failure, and is therefore to be met with in conditions of fatigue.

I have to thank Major W. R. Edwards, I.M.S., for a record of facts signed by a friend of his, a captain in the R.A.

"At the Assault-at-Arms at Quetta, in June, 1899, the tug of war teams of No. 7 M.B.R.A. and the 6th Bombay Cavalry were the winning teams of the British and Native tugs of war respectively.

"These two teams frequently practised against one another for two months or so before the Assault-at-Arms. The average weight per man of the Mountain Battery team was just over 13 stone, the average weight of the Cavalry team (who were all Sikhs) was about 11 st. 8 lb., under rather than over. At the beginning of the training the Sikh team was so much the better that it beat the Battery team even with the advantage of the ground in favour of the latter. Towards the end of the training the two teams were about equal, the Battery team never being certain of beating the Sikhs. Two days before the Assault-at-Arms a trial was pulled on the most level ground that could be selected, and the result was a victory for the Battery, but only after a magnificent pull of 12½ minutes, in spite of the immense advantage in weight on the side of the Gunners.

"One very noticeable point in the training was that if a Gunner's hands became chafed he had to give up pulling till they were right again; a Sikh managed to continue his pulling whether his hands were chafed or not.

"———— CAPT. R.A.

"*November* 14, 1899."

"On July 29, 1897, No. 7 Mountain Battery Royal Artillery (consisting of about 100 British Gunners and 150 Native Drivers, half Sikhs and half Punjabi Mahommedans) received orders to proceed on service at once to the Malakand, the movement being of the utmost urgency, and to be accelerated in every possible way. The Battery marched the next afternoon to Abbottabad, 15 miles, arriving at 8 p.m. and leaving again at 4 a.m. Owing to difficulties in watering the mules and taking over fresh transport, the men had only a few hours' rest that night.

"The following day a double march to Harripur was made (22 miles), but the heat was intense and a halt had to be made during the hottest hours of the day, and the Battery only settled down in camp at 8.30 p.m.

"A start was made at 3 a.m. the following morning, and Hasan Abdal (21 miles) reached at 1 p.m. This completed a march of 58 miles in 46 hours. The heat was dreadful and the Gunners suffered severely, many having to be helped along in ekkas and on spare mules, though all marched in the last two miles to the Railway Station at Hasan Abdal. Hardly a single Driver fell out the whole march.

"The Battery entrained that afternoon in two trains, the first of which arrived at Nowshera at 1 a.m. the next morning. The half Battery detrained at once, but the platform was encumbered with carts, &c., and the men did not get into camp till 3 a.m. The second half Battery came into camp at 7 a.m.

"All ranks were suffering from want of sleep and from the terrible heat.

"At 9 a.m. orders were received that the Battery was to try and reach the Malakand (47 miles) in 24 hours, as a fight was imminent. The only chance of doing this seemed to be to leave all baggage at Nowshera under a guard, and use the baggage mules to mount men who could march no further. This was done, and the Battery marched at noon on a day hot even for Nowshera in August.

"After marching 5 miles it was found impossible to proceed. Several men were down with heat apoplexy, and riding barebacked

mules was more than the majority of tired and chafed Gunners could do. It was resolved to halt till the evening, sending back the baggage mules to bring up the baggage, while the Battery marched on to Marden (16 miles from Nowshera). The Gunners were far too done to go back for the baggage, so 50 Native Drivers were sent. These 50 Drivers rode the bareback mules back to Nowshera, packed, sorted, and loaded the baggage (150 mule loads) in a dust-storm, and then marched 16 miles to Mardan, arriving there at 3 a.m. and marching again at 7 a.m. It would have been absolutely impossible to do the work with the Gunners—willing as they were, they were utterly tired out; but the 50 Drivers did it cheerfully, and were little the worse for it.

" ——— Capt. R.A."

Major Edwards tells me that the Mountain Battery trained on their ordinary rations, viz., 1 lb. of meat, including bone, 1 lb. of bread, with potatoes, tea, salt, &c., though they no doubt bought some extra food for themselves.

The Sikhs trained on 8 oz. of ghee (butter oil), 2 lbs. of milk, 1 lb. of attar (whole meal) and some vegetables, and once a week as a treat 4 oz. of meat.

The difficulty which the heavier team had in pulling over the lighter one is remarkable, and shows that weight is not always power—it depends what the weight is made of. Major Edwards tells me that the Sikhs are " thin, hard men, not an ounce of spare flesh on them," and we may suppose that the Mountain Battery team had a certain amount of adipose which helped them in weight.

Judging by weight they should have pulled over the Sikhs easily, but their loss of power on the internal work of circulation and nutrition was so great that the power available for external work was less than that of the Sikhs, and this equalised the difference.

One of the results of this internal friction and defective circulation and metabolism in the Gunners was the adipose they carried, for collæmia causing defective combustion, causes also defective combustion of fats and deposition of adipose. This is why butchers are so often stout. The Gunners, though they took probably but little butter carried some under their skins, while the Sikhs, who had 8 oz. of ghee per day—and Major Edwards informs me that this was increased to 16 ozs. for the last month of training—combusted the whole of it, and carried none.

In the other record the endurance of the Drivers was much greater than that of the Gunners. The conditions here were not quite equal, for no doubt the natives would feel the heat much

less than the Englishmen. But after making full allowance for this, there is still a large margin of difference which only diet and freedom from collæmia will account for.

We can now quite understand how the friction is produced and why the skin circulation, being an index of its extent, is quick in those who endure and slow in those who fail; also why the uric-acid-free diet soon doubles and trebles the endurance of those who follow it.

For the record of a tug-of-war in which Sikhs beat British sailors, see the *Waterloo and Crosby Herald*, January 4, 1902, a reference to which I owe to Dr. Little of Liverpool.

Cases of fatal fatigue (see paper by Dr. Dukes, *Lancet*, 1893, vol. i., p. 1136) present, I believe, only an exaggeration of the above-named symptoms, and even the disintegration of the blood he mentions may be but a further stage of the blood changes producing the albuminuria noticed by Mahomed, or the blood changes in anæmia, of which I speak presently, or the still more marked changes in the blood seen in paroxysmal hæmoglobinuria, which I believe to be paroxysmal collæmia (see chapter xii.).

The same explanation applies to a case recorded by Dr. Lee Dickinson (*Lancet*, 1894, vol. i., p. 1250), where transient hæmoglobinuria followed muscular exertion taken while out of training.

The fact that fatigue means an excess of uric acid in the blood (collæmia) suffices to explain its relation to acute rheumatism. Let there be exercise and perspiration, with increased alkalinity of the blood and collæmia as its result, and let there supervene on this cold or fever which causes a sharp rise in the acidity of the urine and an equally marked fall in the alkalinity of the blood, and we have all the factors in the natural causation of acute rheumatism.* The sharp fall in alkalinity will drive the uric acid out of the blood into the joints, and the effects there will correspond to the amount of uric acid in the blood and the rapidity with which it is driven out.

Thus the effects of uric acid enable us to account for every symptom and pathological relationship of fatigue. But fatigue pushed to extremes produces syncope, and this syncope may continue and end in death, as in the case recorded by Dr. Dukes.

The causation of this syncope is that, from causes which differ from physiological conditions merely in degree, the blood is flooded

* See also Dr. A. S. Eccles, *British Medical Journal*, 1891, vol. i., p. 1075; also "The Practice of Massage," by A. Symons Eccles, Macmillan, London, 1895, pp. 85 and 198, where many interesting facts about fatigue and rheumatism and their relations to other conditions are mentioned.

with uric acid. This obstructs the capillaries, hinders the circulation through the muscles, nerve centres, lungs, and other organs, and produces high blood pressure and alteration of heart sounds as in the case recorded by the late Dr. Mahomed.

If collæmia gets more severe the heart falters and flutters, as I have noticed that it does in these circumstances in myself (see fig. 37), and finally, if there is no relief it stops, and syncope supervenes. Syncope is no rare occurrence in severe attacks of the uric acid headache itself. Speaking of dilatation of the heart, Sir W. H. Broadbent says: "It is usually gradual in its development, but acute dilatation of the heart is a more common occurrence than is generally supposed, *and when it is induced by effort, antecedent high arterial tension is, according to my experience, a constant predisposing factor*" ("The Pulse," p. 168).

It appears to me that we have possibly in what is called "Family periodic paralysis"* a pathological exaggeration of certain of the symptoms and results of fatigue, for it appears chiefly after muscular exertion, it is accompanied by marked increase of cardiac dulness, and there may be some signs of debility or even of syncope, while it passes off after rest.

The mere fact that it is periodic suggests possible relationship to the great periodic circulation diseases, migraine, epilepsy and depression, and that it runs in families is a further point of resemblance to the markedly hereditary migraine.

The explanation given of the "acute increase" of cardiac dulness during the attack is that it may be due to pericardial effusion, but I think it is much more likely to be due to acute dilatation resulting from collæmic high blood pressure, for we can understand this disappearing rapidly; while a similar clearing up of a pericardial effusion is more difficult to credit. Fatigue will produce syncope, even fatal syncope, and in these cases the blood pressure is high, *i.e.*, the syncope is produced by obstructed capillaries which the heart fails to force.

Possibly sufferers from periodic paralysis have somewhat weak and small hearts which dilate easily before the collæmia of fatigue.

I have seen several cases of temporary paresis of the lower extremities in adults which I could only attribute to defective circulation in the cord due to collæmia and heart failure, of both of which I had evidence. But if I am right collæmia and high blood

* As in the cases described by Dr. E. F. Buzzard in the *Lancet*, 1901, vol. ii., p. 1564.

pressure could easily be demonstrated with the increased area of cardiac dulness and the onset of the paralysis in these cases of periodic paralysis.

It would be interesting to know whether any of the sufferers were large consumers of such things as flesh, tea, coffee, or pulses. Compare with Dr. Handson's case of chronic paralysis recorded in chapter xiii.

If the syncope of fatigue has this causation it seems probable that syncope met with under other conditions may be similarly produced.

I have already (chapter vii.) mentioned the pulse of epilepsy and other convulsions, its slowness and high tension, and the late Dr. Moxon's suggestion that stoppage of the heart is the cause of the fits. My own experience shows that the heart specially flutters and falters as blood pressure rises. I have also mentioned the syncope of bathing. There is another condition in which syncope is not uncommon, namely, convalescence from acute disease, and here also it is associated with high blood pressure and subnormal temperature as in fatigue. I make it a rule not to allow any convalescent to sit up or make any exertion till the temperature has risen to normal and remains there. I know that the heart is often affected, perhaps dilated, by the high blood pressure, and that any effort may be the last straw.

This throws light on the causation of Bright's disease, so often originating in post-febrile conditions, especially after scarlet fever.

Now post-febrile collæmia with its signs of slow capillary reflux and sub-normal temperature, means in any case defective metabolism and combustion; but if in these circumstances the heart fails before the collæmic obstruction of capillaries, we get at once the most defective circulation and combustion compatible with continued life, and it is little wonder that under these conditions some albumens fail to be metabolised and are excreted unchanged in the urine.

It is clear then that heart failure is a most important determining cause of acute Bright's disease, and the dropsy which accompanies it is a sign of its origin. If the heart did not fail the collæmia would cause considerable damage to normal combustion; but when it does fail the damage must be trebled and quadrupled, and dropsy is added. Heart failure is thus second in importance only to the collæmia itself.

There is one other condition in which syncope sometimes occurs, namely, during or just after the administration of chloroform. I

think this has many points in common with the conditions named above, though, as I have no personal experience worth mentioning, my remarks are only suggestive.

Chloroform frees the capillaries and lowers blood pressure (as appears to be well known), and I think it may do this (like so many other drugs mentioned in this volume) by clearing the blood of uric acid. We may also call to mind that the mental excitement, hysteria or delirium met with in certain stages of anæsthesia are the results of this fall of blood pressure.

When the chloroform is stopped there will be that rise of blood pressure which I have spoken of as the rebound, and if this is great and rapid the heart will flutter and falter and perhaps cease to beat.

It is interesting to see that Mr. J. P. Lockhart Mummery (*Lancet*, 1905, vol. i., page 778), quotes a chart from Blauer showing that administration of chloroform is followed by a fall in blood pressure. In such observation as I could make I have found that chloroform causes a quickening of the capillary reflux and it would thus probably cause a fall of blood pressure, as do all substances quickening this reflux. I do not for a moment deny that chloroform may cause syncope by weakening the muscles of the heart, and that such syncope may often occur during administration of chloroform; but the syncope of which I speak occurs after the chloroform has been withdrawn, and is, I believe, due to the rise of pressure following this withdrawal—the rise which corresponds with the slowing of the capillary reflux, which in turn is no doubt due to the return of a more or less large quantity of uric acid into the blood.

The fluctuation in blood pressure which the drug produces will be greater (other things equal) the more uric acid there is in the body and blood when it is administered, and the greater the fluctuation the greater the strain on the heart.

Taking this view I was interested in an article by Dr. R. Kirk, in the *Lancet*, 1893, vol. ii., p. 429.

He shows that in animals when inhalation of chloroform is discontinued the lungs are emptied of its vapour in 10—20 seconds, and a little after this the heart suddenly slows and becomes irregular, and there may be syncope. Further, the longer the inhalation is continued, the later does this slowing and irregular action of the heart appear, and he says, "the irregular action commences when the last drop of chloroform has left the blood."

This disposes of any idea that the irregular action is due to the chloroform, but if due to the rising pressure as I suggest, it almost amounts to a demonstration.

If the heart fails rapidly its action may become quick instead of slow, just as in other conditions where there is high blood pressure (see chapter v.).

And with this failure of the heart the blood pressure will fall very greatly; but that there is rising blood pressure at the onset of the trouble is, I think, proved by the slowing of the pulse, in accordance with Marey's law (see chapter v.). While if the first event is a great fall of blood pressure as Dr. Kirk seems to suppose, there is no reason why the heart should slow, and I have just pointed out that blood pressure is high and pulse slow in the parallel conditions of fatigue, convalescence (post-febrile brady-cardia), and certain cases of epilepsy.

Post-chloroformal high tension differs from these chiefly in its rapid onset, and it is on this account more likely to affect the heart severely.

Some cases bearing on these points were published by Mr. A. Wilson in the *Lancet* of November 17, 1894, and in a paper on "The Pathology of Chloroform Syncope" in the *Lancet* of February, 1895, I have referred to these and others in illustration of my argument.

In Mr. Wilson's Cases 1 and 2 we have, as he truly says, all the signs of primary failure of the circulation, and in Case 6 this occurs as the patient is coming round and is sufficiently conscious to give a cry of pain, but whether in Cases 1 and 2 the syncope came on during slight breaks in the administration of the chloroform, as contended by Dr. Kirk, there is not sufficient evidence to show. With regard to Case 6, Mr. Wilson remarks that the syncope was due to the reflex inhibition of the heart by pain, but that some blame must also be laid upon the semi-anæsthetic condition of the patient at the time. I shall return to these points. It is interesting to note that Mr. Wilson agrees with Dr. Kirk in looking upon a sudden quickening of the pulse as a danger signal.* Dr. Kirk also mentions the case of a patient who died from "the reaction which ensued when he began to breathe fresh air."

In the *Lancet* of November 24, 1894, there is the record of a case of syncope under chloroform in which nitrite of amyl averted a fatal result, and its effect is said to have been "almost instantaneous." I have elsewhere suggested that this drug acts by reducing the blood pressure and thus freeing the heart from its overpowering effects (for another case in which it was used with success see the *Lancet* of March 7, 1885). In the *Lancet* (November 24, 1894)

* The *Lancet*, June 23, 1894.

there is the record of a case in which death ensued, and it is said with regard to the onset of the fatal signs that "the administration of the chloroform had been stopped," and in an annotation in the next number (p. 1291) further points of interest are mentioned: (1) that she had taken chloroform with impunity on other occasions; (2) that she had been confined fifteen months previously and had recently lost a child, and was suffering from the depressing effects of grief; (3) that there was slight renal disease (and I note also that one of Mr. Wilson's cases suffered from chronic Bright's disease); and (4) that "before the dentist had touched the patient, although the chloroformist had taken away the chloroform from her face and pronounced her ready for operation, she suddenly became ashy pale, but respiration continued"; here, then, we have exactly the condition insisted upon by Dr. Kirk and Mr. Wilson.

Another death under chloroform — in which there was difficulty in giving the anæsthetic owing to the nose being the point of operation, and where the patient, therefore, came round several times before the fatal event—is recorded in the *Lancet* of August 26, 1893, and similar deaths from too little chloroform or a lull in the administration were discussed in 1892 and 1893.* I have mentioned Mr. Wilson's opinion that in his Case 6 the syncope was due to the reflex inhibition of the heart by the pain, but I believe a somewhat different relation between cause and effect is possible. Thus I have said, with reference to the effect of high blood pressure on the action of the heart (fig. 37), that my own never falters or flutters except with high or rising blood pressure; but there is one other condition in which it does this just as in pulse tracing A, fig. 37 (which shows well-marked high blood pressure), and that is during severe irritation of a sensory nerve. I suffer many things with the dental branches of the fifth nerve, and I have several times noticed that with the most severe paroxysms of pain my heart falters and flutters just as it did when the above-mentioned pulse tracing was taken, for these cardiac irregularities, not being habitual, are always distinctly felt. Now, in my own case, was this a reflex, or was it due to rising blood pressure? If we may consider—and so far as I know, physiology does not negative the idea—that irritation of a sensory nerve causes a general contraction of arterioles and a rise of blood pressure, the cause was in both cases the same; and my heart fluttered under the dental pain for the same reason that it did so in pulse tracing A, because in both there was high and rising blood

* *Brit. Med. Journal*, 1892, vol. i., and 1893, vol. ii., p. 1452.

pressure. We can now fully appreciate the bearing of Mr. Wilson's Case 6. Here the patient was coming out of the chloroform anæsthesia, and blood pressure was therefore rising; suddenly to this was added severe irritation of the sensory nerves of the knee, causing an acute rise of blood pressure, and it was little wonder that the heart was thus completely overpowered and syncope at once resulted. Death may no doubt occur when the heart is weak from the blood pressure effects of pain alone, as in a case recorded in the *Lancet*, 1896, vol. i., p. 1457, where death occurred a few minutes after the extraction of a tooth without anæsthetic.

With reference to the effects of pain on the blood pressure I have had a case in which I could observe points of interest; it was that of a man in whom I had lowered blood pressure by drugs. When the blood pressure had been reduced to 120 the patient got a severe inflammation round the stump of a damaged tooth, his temperature rose to 101° or above, and he suffered considerable pain. While in this condition I observed his circulation factors as usual, and found that (as I should have expected with fever and quickened pulse rate) the capillary reflux was fast (4) but the blood pressure in place of being lower (as one would have expected, say 90—100, owing to the fever and the free capillaries) was 120, *i.e.*, as high as at my previous examination.

I have little doubt that this high blood pressure in spite of free capillaries was effected by pain setting in action the muscles in the coats of the larger vessels and thus raising pressure.

This is a protective action of nature, for if the blood is not turned on full, the pressure at the seat of pain and inflammation will be less.

Doubtless there are two causes of high blood pressure: (1) obstruction of capillaries by colloid uric acid, which goes with slow capillary reflux and is by far the most common and enduring cause of high blood pressure; and (2) contraction of the muscular coats of the arterioles and larger vessels under direct or reflex influence of the nervous system, which may produce some rise of blood pressure quite apart from the existence of any great obstruction in the capillaries. As the above case shows, the instruments and methods we use will quickly enable us to distinguish the conditions.

I agree with Mr. Wilson that one cause of death after chloroform is syncope, and endorse his valuable suggestion that syncope under other conditions should be studied to illustrate this point. If this is done many will be astonished to find how large a number of syncope cases are preceded or accompanied by evidences of

collæmic capillary circulation and its results, high and rising blood pressure (see previous quotation from Sir W. Broadbent, "The Pulse," p. 168), and by excess of uric acid in the urine and blood, if these can be examined.

In the *Lancet*, 1896, vol. ii., p. 881, is recorded a fatal case under chloroform at the Royal Victoria Hospital, Netley, in which all the conditions seem to have been narrowly observed.

It proceeds: "The breathing continued to be natural and regular for about one minute after the administration was commenced; the patient then made some slight attempt to cough and the breathing became irregular," and further on: "Immediately the breathing became affected the inhaler was removed," and again: "The moment the respiration became irregular the administration of the drug was stopped; a few seconds later the pupils dilated and the heart's action ceased, and the man was practically dead, although respiration continued for a few seconds longer."

The error here was the stopping of the chloroform, and everything that followed, including death, was the result; a few seconds later there came the vapour reaction of Dr. Kirk, or what I call the rebound, with rapid rise of blood pressure, and being unable to overcome this vascular obstruction the heart failed and respiration continued, though it had been the first thing to become irregular, showing that in the first instance the respiration had not been really seriously affected.

For very similar records see *British Medical Journal*, 1899, vol. i., pp. 468 and 661, and 1899, March 25, but in none of them is there any explanation given of the fact that syncope occurred *after* the chloroform was withdrawn.

Dr. Kirk's experiments on animals show us that this rebound is best prevented by at once resuming and steadily continuing the chloroform, by the sudden withdrawal of which it was occasioned.

It seems probable from these considerations that the less the quantity of chloroform given before it is withdrawn the sooner the rebound comes, while the longer the administration and the greater the quantity administered, the later the rebound. Hence it is probably more dangerous to suddenly withhold chloroform early in its administration, as in the above case, than later on. This explains the observation of some anæsthetists that more patients die from too little chloroform than from too much, and the by no means infrequent records in fatal cases that special care had been taken to give very little chloroform.

In the above case it seems probable that if the slight irregularity

of the respiration and cough had been disregarded, and the chloroform quietly and carefully continued, the cough would have subsided and the anæsthetic could have been continued throughout the operation. Then in the rebound (when chloroform was discontinued at the end of it) the rise of blood pressure would have come gradually, and the heart would not have been overpowered.

Brig.-Surg. Lieut.-Col. Stevenson, who records the above case, mentions that he has seen another in which "the sequence of events was precisely similar; the pulse first stopped, then the respiration," showing how very frequent, relatively to fatal accidents with chloroform, such cases are. What I have suggested is a most simple deduction from the records of Dr. Kirk's experiments.

Writing to me, Dr. Kirk mentions that further investigation seems to show the blood pressure does not fall as the heart slows; in other words, the heart slows because there is high blood pressure in accordance with Marey's law; but if the heart falters because it cannot overcome the obstruction and the high blood pressure, if its systoles become imperfect and its action irregular, or still more if it stops altogether, of course there is a fall of blood pressure.

The effect of high blood pressure on the heart is then either quick action or slowing; the former if it fails, the latter if it is able to withstand it, and obviously the higher the pressure the more likely is it to fail and quicken its action (tachycardia). This is exactly what Dr. Kirk's results with animals show; with the highest blood pressure the heart's action is quick and irregular, with a slight fall of blood pressure it slows.

This is exactly what we see in epilepsy in cases where, as observed by the late Dr. Moxon, the heart stops. In these cases the heart has been seen to act slower and slower, and then it stops altogether (an exaggeration of the dropped beat in my own pulse, fig. 37), and the patient falls insensible and convulsed from stasis and anæmia of the brain. A great fall of blood pressure follows, so that a wound ceases to bleed (as in the case of epilepsy previously mentioned in chapter vii.); this fall of blood pressure relieves the heart, and it begins work again if the cerebral centres have not lost their functional activity; but if anything prevents it from starting again death ensues. Bleeding, as in a case of post-chloroformal syncope recorded in the *British Medical Journal*, 1896, vol. ii., p. 122, may relieve the heart by permanently reducing blood pressure, and in this case also the pulse stopped before the respiration.

Hence in such cases of post-chloroformal and other syncope from high blood pressure, holding the head down as the lowest point of the body gives the medullary centres some little blood, and possibly saves their functional activity till the heart has time to recover itself.

Dr. Kirk says that in his experience rabbits (herbivora) are not liable to the irregular action of the heart when chloroform is withdrawn, while dogs and cats (carnivora) are very much so, which is again very strong proof of the causation I am suggesting.

For though the muscles of herbivora no doubt contain xanthin as we get excess in our body from eating them, this is merely a small residue remaining unexcreted at the time of death, and the quantity in their blood at any one time is small.

Another condition in which syncope occurs is in church while kneeling with the arms raised, and Marey points out that this position impedes the circulation in the raised limbs, raises the blood pressure and slows the heart, and here again the slowing may be preparatory to its becoming quick or irregular, or stopping altogether.

Further evidence is, I think, to be seen in the fact that nitrite of amyl is useful in this chloroform syncope, and there is probably no drug which would more quickly relax the arterioles, free the capillaries, and prevent the rise of blood pressure, while it is hard to see how it can do good if the blood pressure is already low.

For the fact that blood pressure falls under chloroform see *Lancet*, 1898, vol. i., p. 1681.

I am reminded of an experiment I made recently to test the effects of nitrites on the diameter of the radial artery. At 12.15 p.m. my pulse being 66, and the radial diameter in the recumbent position 1·0 mm., I took, after making these observations, at 12.20 one compound trinitrine tabloid containing trinitrine and nitrite of amyl. A few minutes later there was a feeling of general pulsation, the radial diameter in the same position was ·9 mm. At 12.28 it was also ·9, but at 12.33 it had increased to 1·1 mm., larger than it was before the drug was taken, and at 12.40 it was 1·0 again, exactly the same as at 12.15. At 12.28 and with the general throbbing the pulse rose to 76, at 12.33 it was 72, and at 12.40 the same. My notes show that between 12.28 and 12.33 there were numerous well-marked intermissions of the pulse which were not present at the observations preceding or following these. I think this is an instance in which the nitrites which so markedly lower blood pressure (as shown both by the sphygmograph and

the arteriometer and which therefore act just like chloroform), like chloroform caused marked fluttering and irregularity of the heart's action as their effect was ceasing and higher blood pressure returning.

We see in this record that the pulse which, in accordance with Marey's law, quickened to 76 when the blood pressure was reduced, remained at 72 when the pressure had again risen higher than before; and this is another sign of some failure of the heart, for I have pointed out that the most marked exception to Marey's law is found in the case of a heart that fails and dilates before high blood pressure, as it then quickens with rising pressure in place of slowing down. My heart in this experiment had been tried by the rising pressure at 12.33, as shown by irregular action, and therefore remained quicker than it was before the experiment, in spite of blood pressure having risen higher.

The same thing is often seen in cases of chronic Bright's disease. Here if we get high blood pressure, and the heart's action is slow (*i.e.*, at or below 60), we have a strong heart which has hypertrophied and become equal to its work, we therefore get no dropsy of any sort, the urine is fairly profuse and of low specific gravity, and if we clear the blood of uric acid and free the capillaries, the heart quickens its rate up to normal or above it.

But if we have a case of chronic Bright's disease in which the heart is failing, we have signs of high pressure in the pulse and the capillaries and the second sound at the aortic base, but the heart may be beating from 80 to 120, and probably fluttering or palpitating as well. Here we have heart failure, and its results take the shape of general dropsy, ascites, congested liver, scanty urine of fairly good specific gravity, in spite of the fact that at the *post mortem* the kidneys are found to be fibrous and granular. In this case if you can free the capillaries and strengthen the heart it will slow down towards the normal rate of action as conditions improve.

I have often personally noticed similar effects produced by taking nitrites, and have no doubt that a similar result could be produced with them any day, especially if taken in the morning hours, but in the above instance the arteriometer enabled me to demonstrate with very considerable certainty the exact relation between blood pressure and irregular action of the heart.

I suggest that we have here possibly a valuable means of testing whether it will be dangerous to give chloroform, namely, by watching the effects of a nitrite on the heart's action.

If in any given case it is proposed to give chloroform on Wednesday at 11 a.m., give on Tuesday at the same hour (the reasons for this are, I hope, now obvious) a nitrite, and if as its effect is passing off, some 10 to 15 minutes after it has been taken, the heart's action shows marked irregularities, that patient has a somewhat weak heart or an excess of uric acid in the blood or both, and it may be dangerous to give chloroform.

For it follows from Dr. Kirk's observations that the effect of chloroform passes off in a few seconds after it is discontinued, and the resulting rise of blood pressure will be more sudden and dangerous, while the effect of the nitrite is more gradual and causes only a little irregularity of the heart's action.

I have to thank Dr. W. Rushton Parker, of Kendal, for the interesting suggestion that my explanation of the causation of chloroform syncope by its effects on uric acid and the blood pressure may account for "the immunity of pregnant women from chloroform syncope as compared with the same women in the *post partum* state. At the Rotunda Hospital, Dublin (where I was obstetric assistant and chloroformist), we administered chloroform for forceps, craniotomy, &c., without the smallest reluctance; but for removal of adherent placenta, or for stitching a torn perineum, or for anything *post partum*, we always felt the risk to be greatly increased."

Dr. Parker considers that this is common experience among obstetricians, and refers to works on midwifery for similar opinions. I was myself a student at the Rotunda, and can distinctly recollect this feeling with regard to the administration of chloroform.

If this is the case, we have an instance in which in a few hours and in the same patient the administration of chloroform passes from safety to danger, in absolute correspondence with a very marked increase in the amount of uric acid in the blood and urine, for I have pointed out (see chapter iv.) that post-puerperal collæmia accounts for some physiological and pathological conditions occasionally met with at this stage of a natural function.

The above-mentioned cardiac failure is accompanied by violent struggling or even convulsions on the part of the animal or patient, which fact is correlated with my explanation of the pathology of convulsions from rising blood pressure in the previous chapter (see also previous remarks on the Pulse of Epilepsy).

When struggling occurs in the course of inhalation it is, I think, the practice of anæsthetists to give chloroform more free

and this is, it appears, the right course, for the trouble is due to failure in the supply of chloroform, which allows the blood pressure to rise.

If the tension effects of chloroform are due to its action on uric acid, and proportioned to the amount of this substance in the blood, we come in view of several facts which admit of explanation. It has, for instance, been suggested that there is more trouble with chloroform in London than in Edinburgh, and we know that gout is common in London and rare in Edinburgh, and there is probably more tendency to excess of uric acid in the blood in the former than in the latter city. Similarly, the vegetarian natives of India may have less risk of chloroform syncope than beef-eating Englishmen, and this carries suggestions as to prevention. I am indebted to Dr. E. G. Horder for the information that the vegetarian natives of South China have a similar immunity, though both in India and China the warm climate which directly prevents or dissolves collæmia may have something to do with the result (see also Dr. Kirk's experiences above-mentioned as to results in cats and dogs on the one hand, and rabbits on the other).

It was suggested in an annotation in the *Lancet* (1889, vol. ii., p. 606), that gout might account for the different reaction of patients under chloroform in Edinburgh, London and India respectively, but no reason was adduced.

I have already (chapter v.) quoted from Marey the fact that alcohol causes a dicrotic pulse, except when it produces gastric disturbance. This by keeping up alkalinity prevents the alcohol from clearing the blood of uric acid.

Alcohol or morphine, so often advised to be given before inhalation of chloroform, may act by clearing the blood of uric acid, and thus preventing a rebound when the anæsthetic is left off. The rebound after alcohol or morphine comes more gradually, and will therefore affect the heart less severely, as is the case with nitrites, but they all affect it to some extent.

Sir T. Lauder Brunton remarks that he has been told by Professor Poehl, of St. Petersburg, that in Russia the presence of an excess of alkaloidal substances in the urine is regarded as a sign that it will be dangerous to give chloroform (*Lancet*, 1893, vol. ii., p. 861), and mentions that he himself had previously entertained the idea that certain alterations in tissue change might increase the danger of chloroform.

There can be no doubt that an excess of uric acid in the blood produces very great alterations in tissue change, and we have

had a well-marked instance in the causation of fatigue. I suspect that the excess of alkaloids noticed by the Russian observers runs parallel with an excess of uric acid (see chapters vii. and x. to xiv.).

I often observe that conditions in which increased toxicity of the urine is described are very frequently conditions in which my experience tells me there must also be an increase of uric acid in the blood and urine, and I suggest that the quantity both of uric acid in relation to urea and of alkaloids should in future be observed in the urine before operations under chloroform.

After pneumonia and also after typhoid fever the toxicity of the urine is said to be high (*Prog. Méd.*, April, 1899, pp. 277 and 296), and after both there is an excessive excretion of uric acid, and all the signs of its excess in the blood. What I have said about menstruation, with figs. 31 and 32, explains perhaps a case in which chloroform produced a fatal result in a menstruating woman (*Lancet*, 1895, vol. i., p. 237).

As to the way in which an excess of uric acid in the blood may produce these alkaloids, see as regards the intestines, chapter vii., and the causation of oxaluria, chapter xii. I think there can be little doubt that deficient circulation produces a similar effect in the tissues generally. Professor Mosso tells us with regard to the pathology of fatigue, that when it is carried beyond a moderate amount the blood is subject to a decomposing process through the infiltration of poisonous substances (see *Lancet*, 1887, vol. i., p. 1295). There is, I think, no doubt that the blood in fatigue contains an excess of uric acid, and owing to the effect of this on metabolism, other poisons (sulphuretted hydrogen, &c.) will soon be added, though I think that uric acid itself, either directly or by its effects on the metabolism and combustion, causes the decomposition of the blood both in fatigue and hæmoglobinuria (see also chapter xii.).

Another writer mentions that the proportion of alkaloids in the urine during the eight hours after waking is five times as great as in the urine of the rest of the day (*British Medical Journal*, 1886, vol. ii., p. 1271). Now the largest excretion of uric acid and the most marked collæmia occur in these same hours (see fig. 3).

I could give references to further cases in which heart failure occurred after chloroform was withdrawn, as, for instance, in *British Medical Journal*, 1899, vol. i., p. 468.

In some cases (*Lancet*, 1898, vol. i., p. 330) it has been sought to prove that this was due to shock, a matter I have already con-

sidered, but in at least one of the cases there could be no question of shock, as no operation had been performed at the time of the fatal syncope.

For such cases certainly, and for many others probably, there is no satisfactory explanation except that which attributes the heart failure to a sharp rise of blood pressure as the effect of the chloroform passes off, and thus brings post-chloroformal syncope into line with numerous other forms of heart failure.

In one case which I carefully investigated the capillary reflux was slow before chloroform was given, it quickened decidedly during anæsthesia and slowed again after anæsthesia had passed off.

In the preceding pages we have seen that several mental diseases bear a definite and constant relation to changes in the circulation which acknowledge uric acid collæmia as their cause, and that this explains many facts in their causation and occurrence, such as the time and season relations of suicide otherwise almost inexplicable.

That fatigue and the combustion and metabolism of the body (as we shall realise more completely later) are also dominated and controlled by collæmia and its circulation changes, this, again, accounting for most of the relations of fatigue to time and circumstance and its connection with rheumatism, enabling us to say why fatigue is present under some conditions and absent in others, and giving us a correspondingly large and important power of control.

That the circulation effects of collæmia explain the causation of heart failure and syncope under many different conditions, and that post-chloroformal syncope will probably in time take its place among these. I expect further investigation will show that just as chloroform is more dangerous after labour than before, it is also more dangerous in the morning hours than in the evening, and in the presence of menstruation, Bright's disease, &c.

The diagnosis of all these conditions depends on correct observation of the circulation changes and the dependence of these on excess of uric acid in the blood and urine.

The great distinguishing mark of all such diseases as have a circulatory connection with uric acid is that they are temporary and paroxysmal, and fluctuate from day to day and generally from morning to evening in accordance with the physiological fluctuations in the solubility and excretion of uric acid; and while they are still functional control of the uric acid will control the disease.

But to take the case of mental depression, the cause of which is

defective intracranial (cortical) circulation, it is obvious that quite a number of conditions besides those due to uric acid may produce this result. Yet as uric acid is in constant action its effects (slight as they may sometimes be in comparison with those of some organic factors) will add themselves on to those of the organic factor and thus determine the period of greatest depression and its relation to times and seasons as above sketched out.

When the organic factor is a serious one the effects of the uric acid fluctuations are more or less completely overshadowed, periods of intermission will be slight and the prognosis bad.

On the other hand when the fluctuations are large and periods of complete intermission frequent and well marked the organic factor is of less importance, the uric acid factor relatively greater, and the prognosis more hopeful. In all cases it will do good to diminish the uric acid factor, but where the organic factor is serious the relief will be but slight.

This pathology naturally leads to a favourable prognosis in many early conditions of mental disease. The common anatomical factor (large arteries of supply to the brain), far from being a drawback is an actual advantage to the race; supply these arteries with pure blood, and in place of pathological deviations, you have a brain with more than ordinary physiological powers. This probably explains the common observation that the step from great mental power to insanity often seems short; for the anatomical conditions producing great mental power also prepare the brain to be seriously affected by impure blood, high blood pressure, and by heart failure in the case of general paralysis (for some interesting records of facts with reference to these points see "Mental Affections," by Dr. Macpherson, p. 25).

The indications for treatment are practically the same as those for the collæmia of headache, bearing in mind that collæmia which produces mental depression is very often secondary to other conditions, such as dyspepsia, debility after parturition, prolonged lactation, or fevers, or accompanies progress of new growths or other organic disease. It is useless to treat collæmia without attention to its cause, though in any case a diet which diminishes the intake of urates will probably do some good, for the more the available urate the greater and more lasting is the interference with metabolism and nutrition.

A craving for animal food at an early age in children is by some regarded as a sign of impending insanity, and it is said that children naturally do not crave for it (see *Lancet*, 1896, vol. ii., Dr. McNeill).

Similar remarks made by Dr. Clouston have interested me because I have often noticed a similar craving for meat in epileptics, and to my mind this is often due to the temporary relief thus afforded to the high blood pressure of collæmia.

I think our knowledge of the causation of fatigue may be of use to soldiers and sailors, or those called upon to make exertions on which their safety and that of others may depend. It also explains the well-known use of opium by the natives of India.

Muscular strength is of little avail if it cannot be brought into play, and the man who in an early stage of exertion has the circulation through the muscles so much obstructed that waste products are slowly removed and his heart fails and dilates before rising blood pressure, will be overcome by a better trained antagonist.

The fall of urea which exercise produces is the measure of this clogging with waste products. The rise of urea next day represents the washing out of these waste products, when the circulation through the muscles is again freed from uric acid.

Clearing the blood of uric acid is a substitute for training and by freeing the circulation through the muscles allows of an immediate removal of waste products, as shown by an immediate rise of urea in place of a fall, for while this lasts there is no fatigue, and the muscles are capable of comparatively unlimited activity. (See Prof. Irving Fisher, *Yale Medical Journal*, March, 1907.)

The power to produce this condition may often make the difference between defeat and victory, and, if muscle power is good, puts an untrained man on a par with a trained one.

There are not a few cases in which otherwise good lives are lost owing to heart failure and syncope before the high blood pressure which fatigue induces, and a timely use of opium, mercury, or any other drug that will keep the blood clear of uric acid, might suffice to save them.

Major W. R. Edwards, I.M.S., informs me that some of the native horsemen of India are in the habit of giving opium to their horses after a hard day's work, stating that otherwise the horse will not sleep, will go off its food and be useless next day.

This is exactly what occurs in man, fatigue, collæmia, high blood pressure, and sleeplessness; but if the capillaries are freed and the blood pressure lowered by opium or mercury, sleep comes naturally. We must also remember the effect of a free capillary circulation on the nutrition of the muscles. I have already referred to the fact that horses suffer severely from rheumatism, which is in some respects an exaggeration of fatigue and stiffness.

It would be worth considering whether the evil effects of heat are not, to a large extent, the result of the collæmia it occasions, and whether the use of drugs which keep the blood clear of uric acid would not diminish them. Indeed, the use of opium by the natives of India almost amounts to proof.

In my own case the previous clearing out of uric acid by a course of salicylates prevents—at least for some hours—the usual depressing effects of exposure to heat and exertion.

Persons who are free from uric acid excess can certainly endure warmth without resulting fatigue, and can take alkali or alkaline foods with relative immunity from depression.

When the day of exertion is fixed salicylates can be used as in fig. 49, but the more useful method is to employ a drug which directly interferes with the solubility of uric acid in the blood; especially a metal like mercury, with which it forms an insoluble compound. This can be carried in the pocket and taken as required just before or during exercise.

The action of these last-named drugs, unlike the salicylates, will be followed by a rebound when they have been left off for a few hours; but this is a small price to pay for winning a victory, or saving a life from syncope.

Where syncope occurs under such conditions as suggest a relation to possible excess of uric acid in the blood, the power of drugs or diet in keeping it clear should not be forgotten.

The use of chloroform as an anæsthetic seems to be contraindicated by the presence of headache (migraine), mental depression, fits, high blood pressure, Bright's disease or albuminuria, diabetes or glycosuria, and in physiology, *post-partum* conditions, fatigue or menstruation, though in all these cases effects will depend upon whether the heart is strong or is beginning to fail before high blood pressure. In this last-named condition it may be most dangerous.

It is necessary to mention that the effect of a uric-acid-free diet on my own power of endurance has been enormous; only those who experience it can fully understand my meaning.

I do not exaggerate when I say it has restored my bodily powers to the level of fifteen years ago; indeed, I scarcely believe that even then I could have undertaken my present exertion with freedom from fatigue and distress at the time and immunity from stiffness next day. Frequently in recent years I have got up from a week or more of sedentary work and ridden on a bicycle from fifty to eighty miles without fatigue, other than a little soreness from the unaccus-

tomed saddle, have been able for ordinary work the rest of the day, and next day quite fit to do the same. Many others have now had similar experiences.

Formerly I could do nothing of this kind, especially in spring (the first warmth of the year), and when out of training; then, (especially if the wind was warm and perhaps moist), one and a half or two hours' work would find me in a position of considerable distress from fatigue. Indeed, I often say that it is now impossible to tire me, and relatively I believe this is true. I have already referred to the fact that heat does not affect those who have cleared the blood of uric acid by means of salicylates, and the same holds when it is cleared by diet.

I have no doubt, as I have pointed out in "Diet and Food," that shock or the condition of severe collapse and asthenia that follows on attacks of gastric dyspepsia or gastritis or supervenes on severe abdominal or other visceral injuries, is due to a stoppage in digestion and absorption of albumens producing a corresponding fall in production of force and urea, and consequent flooding of the blood with uric acid—collæmia.

The asthenia of collæmia is partly due to such stoppage of digestion and absorption with falling urea, and partly to heart failure, which, when it occurs from want of nourishment and rising blood pressure, renders the condition much more serious. Digestion and the absorption of albumens re-established, urea will rise and collæmia clear up, and the shock passes off. This pathology applies to all conditions of shock and to the coma and similar lethargic states met with in diabetes, which I shall discuss in chapter xiv. With reference to gastritis and dyspepsia I have shown that nitrites relieve the condition of asthenia which severe diarrhœa produces in children, and which is often accompanied by a rising temperature in the rectum.

Indeed, it characterises all conditions of shock and collæmic collapse or asthenia, the capillary reflux is slow, and temperature in the rectum is considerably above that in the mouth or axilla.

In primary heart-weakness and failure blood pressure is low, and temperature falls everywhere, in the rectum as well as in the mouth. In heart failure before collæmia the heat is shut in in the great cavities, and temperature in the rectum is far above that on the surface, while we have a further sign of obstructed circulation in the fact that blood pressure is below its normal relation to the capillary reflux (*e.g.*, capillary reflux 8 and blood pressure only 140, see p. 326).

Such a patient is depressed when the heart is strong, but tends to become hysterical or excited when the heart fails or is weakened by fatigue. Hence, no doubt, the observation of M. Féré that "One can change a normal into an hysterical individual by tiring him," and uric acid, which increases fatigue, must also increase the tendency to hysteria.

It follows that those who have practically no available uric acid to produce collæmia as urea falls, are, to a large extent, immune from conditions of shock and asthenia that would otherwise supervene upon severe visceral disease or injury, or even on such less marked troubles as dyspepsia, anxiety, or fear, and this I suggest explains the wonderful records made by the Turks and other more or less uric-acid-free nations.

Major W. R. Edwards informs me that though he could probably tire out a native of India on one day, the native could do the same the day after, while he, Major Edwards, is stiff and sore, and needs a prolonged rest.

This is remarkable, especially when it is remembered that these natives have frequently an insufficient supply of nitrogen; but this we must also remember, favours the elimination of uric acid.

It is becoming common knowledge among athletes that meat is not the best food for training, and some of the more advanced, as Mr. E. H. Miles, of Cambridge, for several years the tennis champion of England, have abandoned it; the facts and experiments here recorded sufficing to explain their experiences. Mr. Miles has now given the effects of diet in his own case in a book, "Muscle, Brain and Diet" (previous reference).

In "Diet and Food" I have already referred to the feats of Karl Mann in Germany; and vegetarians in this and many other countries have now established frequent records. The explanation of this fact lies on the surface and can be seen and estimated from the circulation in the skin, and there is thus good reason to think that those who adopt a correct diet in early childhood may escape many functional and organic troubles, just as they will escape unnecessary heart strain, syncope and fatigue.

CHAPTER IX.

Asthma and Bronchitis.

I will begin this chapter with a few remarks on the common cold. My point with regard to it is this—how far is it due to changes originating within the body, how far to external agencies?

A cold may run through a whole house; in this case in so far as B's cold was due to proximity and contact with A it was due to agencies external to his (B's) body. But there are other factors, for B does not always take A's colds; it is only when he is a little out of sorts or suffers from dyspepsia or other small causes of trouble; at other times he may entirely escape. In the same way persons in training for athletic purposes rarely take colds.

It is common experience that women are specially liable to take cold at their menstrual period, when they are also more liable to dyspepsia, gastric upset, bilious attacks, &c.

It is therefore evident that in a common cold we have two factors, (1) altogether external to the body, and (2) originating in certain disturbed conditions of digestion, nutrition, and metabolism inside the body. If 1 does not coincide with 2 no disease results.

The meteorologists in charge of the observatory on Ben Nevis have given us (*British Medical Journal*, 1895, vol. i., p. 248) an interesting account of their experiences with what they call the Ben Nevis cold. It appears about forty-eight hours after descent from the observatory, they have no colds while at the top of the mountain, and if they go up with a cold it ceases.

There is no doubt about the infection; they ascend the mountain with a cold, and it does not spread to others; they descend without a cold and very often get one. On the high level they are braced up by the cold, *i.e.*, the blood is cleared of uric acid by the falling alkalinity which the cold air produces, hence as we have seen in the last chapter, the fires of life will burn strongly and brightly, and the

microbes are rendered innocuous. But the uric acid is not eliminated; it is retained in the various organs and tissues, and, as they descend to the more relaxing climate of the lower level, the alkalinity of the blood rises, this uric acid is got into solution and passes through it. They are now in parallel case to that of a menstruating woman, and the body is in a state of collæmia favourable for the reception of the microbe (see fig. 31).

For the parallel effects of high altitudes and their dangers in cases of collæmic high blood pressure and the value of uric-acid-free diet in such conditions (see *Lancet*, 1899, vol. i., p. 1628).

The same thing is observable in such climates as that of the Engadine. Colds are immediately thrown off, are not taken, or are of the slightest. "The Ben Nevis cold" is really a slander on the mountain, for it protects from cold, but does this by storing up a certain amount of uric acid, which on descent will pass through the blood and produce unusual liability to infection.

Dr. Solly tells us (*Medical Climatology*, Philadelphia and New York, 1897, p. 39) that cold increases muscular power, and (p. 66) that dry cold air is stimulating when the temperature is not too low. A very low temperature may extinguish the fires of life, but short of this it feeds them by putting an end to collæmia and producing free capillary circulation. The author also tells us (p. 164) that the first effect of high altitude upon migraine and epilepsy is beneficial. Of the latter he says, "the strong tonic and alterative qualities of altitude are often of the greatest service." The patient will be kept relatively free from collæmia as long as the "tonic" effects continue; but after that he will relapse.

It must be common experience that a cold is often greatly improved or, if treated early, cured by a good purge. I believe the internal condition which allows the external factor to act is often some intestinal condition which is put right by a purge. Similarly, a dose of wine negus, of spiritus ammon. aromat., and sp. æther nit., or of pulv. ipecac. co., at bedtime, have cured or cut short many a cold; they all clear the blood of uric acid, and free the capillaries, quickening metabolism and combustion.

A further instance is that people in training rarely or never get colds, but when they have given up training they not only take colds, but have them badly.

Such is, I believe, the origin of all colds; a predisposing condition produced by collæmia, viz., a damping down of the fires of life, plus a microbe; and this predisposing factor is probably common to a large number of infectious diseases, such as phthisis

and the exanthemata, and explains the fact that a man may be exposed to a disease many times without taking it, until it catches him some day in a state of defective combustion. We see the same thing in children, who come to the out-patient room one week with diarrhœa and the next with bronchitis. Here the diarrhœa causes collæmia, and collæmia will render them liable to catarrh. Again, teething and its gastro-intestinal disturbances predispose to catarrh, so that some children have bronchitis with each set of teeth, seldom reversing the order.

We can therefore prevent catarrh by preventing collæmia. But when once a local irritation has been produced by cold or a microbe acting on collæmia, such irritation can only be cured by solvents, so that correct treatment depends on the exact stage of the process.

Given a collæmia and the microbe, or cold, or both, to precipitate some of the uric acid from the blood on to the mucous membrane of the nose, pharynx, larynx, we have all the factors in causation. A cold is a gout or precipitation disease of a given local surface, and is therefore cured by solvents such as alkalies or salicylates, or better still prevented by uric-acid-free diet. It is the experience of all who have lived for a few years on the diet that colds get less and less and finally disappear, and long before their final disappearance are easily cured or controlled by solvents; an immunity, however, which ceases with a return to uric-acid-containing foods. Cold is therefore, like rheumatism, a local precipitation of urate, and this may be the result of cold acting locally or of a microbe, or of both. This chapter deals with diseases of collæmia (asthma) and precipitation (catarrh and bronchitis), and while the collæmic disease is benefited by precipitants of uric acid the precipitation disease is benefited by solvents. We may therefore notice (at least in some cases) that precipitants, which benefit the collæmic disease, may produce the precipitation disease, while in turn solvents, which benefit the precipitation disease, may produce the collæmic disease. Asthma and bronchitis are so commonly mentioned together that I must plead that as my excuse for placing them in the same chapter, though knowledge of their etiology shows that they belong to different groups.

With cold, as with rheumatism, an important quantity of uric acid cannot be precipitated on the mucus membrane unless there is plenty in the blood, so that before a really successful catarrh is produced there must be collæmia; and this is the reason why those in bracing mountain climates or in training do not suffer from catarrh. They have no collæmia because the blood is cleared by

the bracing climate or by the stimulating action of somewhat excessive food. This explains the common occurrence, that if we have a more or less long frost in January and part of February everybody is well and free from cold, but when the wind changes to a warm sou'wester with rain, everyone is down with catarrh, influenza or rheumatism. This means that the uric acid stored during the bracing weather invades the blood, the microbe flourishes and causes precipitation of uric acid on the mucous surfaces which it attacks. Only those who are very strong or extremely well nourished, and who do not become depressed or collæmic as the result of change of weather, or those who live on a uric-acid-free diet and thus have no available uric acid, are spared by this sequence of events.

In a paper in "Wood's Medical and Surgical Monographs" (New York, February, 1890, p. 359), I said with regard to asthma: "Here we have a possibly functional disorder which, like so many I have mentioned, has long borne a somewhat indefinite relation to gout; since my investigation on uric acid has brought to my notice its action on the capillaries, it has occurred to me that directly or indirectly it may affect the circulation in the bronchi and lungs and so produce asthma. There are not a few points in the history and symptoms of asthma and its onset which may be taken as suggesting its possible origin in a uric acid storm."

My interest was quickened by seeing in the *Lancet** a notice of a paper by Dr. Yavein, of St. Petersburg, in which it appeared that large doses of citrate and carbonate of soda diminished the excretion of water from the skin and lungs, for I already knew that similar does of these alkaline salts would, by increasing the uric acid in the blood, obstruct the vessels in the kidneys and diminish, so long as the excess of uric acid might last, the excretion of water in the urine.

It seemed probable that uric acid not only affected, as I already knew, the vessels of the kidneys and skin, but also the vessels of the lungs, and diminished the output of water, and I began some researches with a view to confirm Dr. Yavein's results, of which I shall speak presently.

Asthma is commonly spoken of as a paroxysmal affection, attacks occurring about 2 a.m. to 4 a.m., when the sufferer has gone to bed well. The dyspnœa is expiratory, and is supposed to depend on a morbid condition of the very small bronchial tubes,

* *Lancet*, 1892, vol. i., pp. 329 and 882.

this condition supposedly consisting of hyperæmia or congestion, with or without the addition of a certain amount of muscular spasmodic constriction.

My researches convince me that asthma represents one of the effects of uric acid on the circulation in the thorax, and that it is paroxysmal for the same reason as migraine and epilepsy, in accordance with the natural fluctuations in the excretion of uric acid and the amount of the substance traversing the blood.* Clearing the blood of uric acid is the point requiring attention in its treatment, and drugs useful in this disorder have this effect. Furthermore, they are the same drugs as are successful in migraine and epilepsy.

My first point is the relationship of the asthma attack to the excretion of uric acid.

My attention was directed to it by the similar effects of diet in migraine and asthma. I was myself a sufferer from migraine; when on ordinary meat diet I used to have about 30—40 attacks in a year, and on extra meat diet at Oxford for purposes of training (a very dangerous process in my case) the attacks were more frequent and severe. I learned from one of my fellow-students (the late Dr. W. E. Steavenson) that his asthma attacks had been affected in the same way by the training he had done at Cambridge. He suffered from eczema and bad headaches and had had acute rheumatism, while his pulse was often slow and of high tension.

I have had attacks which, if not strictly asthmatic are closely related, and before I recognised this relationship they used to cause considerable uneasiness by suggesting more serious disease.

I noticed that occasionally in the early morning I had a feeling of heaviness or tension behind the sternum with wheezing in the chest, followed by the expectoration of a little mucus; I also noticed that the pain invariably disappeared soon after breakfast, though pain and wheezing occasionally returned about 5 or 6 p.m., to disappear again after dinner.

What specially struck me was the comparative suddenness with which the pain came and went, and the fact that there were no signs of catarrh at other times of the day.

In the course of an experiment undertaken for other purposes, I increased very greatly the excretion of uric acid and the amount passing through the blood; and found that my chest pain and

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* *Brain*, Spring and Summer Number, 1893, p. 230.

troubles were very decidedly worse. When, later on, I reversed the process and cleared the blood of uric acid, so that there was a very small excretion for several days, my chest troubles suddenly disappeared and remained absent until one or two meat and wine dinners with friends increased the uric acid and brought back a morning wheeze.

This opened my eyes, and I was able to explain the periodicity of my trouble; for the largest excretion of uric acid occurs in the early morning hours before breakfast, and the next largest in what I have spoken of as the afternoon alkaline tide, from 3 to 6 p.m.

Again, the onset of the attack in the early morning hours, just when the acid tide of the night is coming to an end, and the excretion of uric acid is rising (figs. 2 and 3), the fact that it tends to be better in winter, when the excretion of uric acid is low, and worse in the spring and summer,* when excretion is high and rising (fig. 4), are points in which it resembles migraine, mental depression, and many uric acid troubles.

Asthma, again, improves during pregnancy unless there is much vomiting, and this is easy to explain, for pregnancy entails a general increase of metabolic activity, which results in a rise of urea and a corresponding rise in the acidity of the urine and fall in the alkalinity of the blood, rendering it a bad solvent of uric acid. Vomiting will, however, reduce urea and acidity, increase the alkalinity of the blood and flood it with uric acid.

In this relation to pregnancy asthma is the parallel of migraine, epilepsy and Raynaud's disease, for all these troubles are generally absent during normal pregnancy, but return afterwards.

I have been told, among others by the late Dr. Steavenson, that the asthma attack is often followed by a diuresis. Here again the parallel with migraine, epilepsy and Raynaud's disease is absolute; and this proves to my mind not only that the capillaries are free after the attack, with a low excretion of uric acid in the urine, but also that they were obstructed during the attack, causing a retention of water in the body which takes the first opportunity of passing off as soon as they are again free.

That the attack of asthma is followed by a diuresis proves, just as in the case of headache, epilepsy and Raynaud's disease, that it was accompanied by a plus excretion of uric acid, with high blood pressure and scanty urine.

There can, I think, be no doubt about the relationship of the

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* See *Progrès Médical*, January, 1890, p. 73.

asthma attacks to a large excretion of uric acid, or to the high blood pressure which its excess in the blood produces, and there are other reasons for this opinion.

With regard to the researches of Dr. Yavein, showing that alkalies diminish the output of water from the lungs, I made experiments comparing the excretion of water from the kidneys with that from the lungs in a given time.

I could control the excretion of water from the kidneys by acting on the uric acid in the blood, and increasing or diminishing its quantity, and I argued that if alkalies, which diminish urinary water by increasing the uric acid in the blood, diminish also the excretion of water from the lungs, I could control the excretion of water from the lungs as well. My researches, so far as they go, seem to show that, to a certain extent, this is the case.

I measured the urine passed in 15 minutes, and estimated, by means of tubes filled with calcium chloride, the water from the lungs in 5 minutes, generally in the middle of the 15 minutes in which I estimated the urine; I then divided the urine passed in 15 minutes by 3, and compared this with the water given off in 5 minutes from the lungs (see chapter xviii.).

I followed first of all the natural fluctuations in the urinary water, and then produced fluctuations by means of drugs affecting uric acid.

In Carpenter's "Physiology," Ed. viii., p. 482, it is stated that from 7—11 oz. of water are daily thrown off from the lungs, the exhaled air being saturated with water, or nearly so. The quantity varies with the rapidity of respiration, with the stage of digestion, and rest or activity, &c.

Taking the quantity as 11 oz., and the urine as 52 oz., we get a relation of 1 part of water from the lungs to 4·7 parts from the kidneys.

The following results were obtained generally about the same hour of the day and at rest, so as to eliminate as far as possible effects of digestion and of exercise.

I also made similar experiments on ten other days at times when the urine was very profuse, *e.g.*, from 10—18 cc. in the 5 minutes; and in none of these did the water from the lungs rise to a corresponding extent, probably because the expired air was saturated and no more water could therefore be given off by the lungs. On these days one got relations of 1—10, 1—12, and even 1—14. That is to say, for obvious physical reasons, the water expired from the lungs cannot rise beyond a certain point.

Date 1893			In five minutes. Water from Lungs grams.		Water from Kidneys cc.		Relation
Feb.	1	..	1·169	..	4·5	..	1-4·8
,,	2	..	1·497	..	7·0	..	1-4·6
,,	3	..	1·514	..	6·0	..	1-3·9
,,	4	..	1·560	..	6·1	..	1-3·9
,,	8	..	1·670	..	7·3	..	1-4·3
,,	10	..	1·367	..	6·0	..	1-4·3
,,	17	..	1·310	..	5·6	..	1-4·2
,,	18	..	1·466	..	6·3	..	1-4·2
,,	18*	..	1·515	..	7·6	..	1-5·0
May	10	..	1·186	..	4·6	..	1-4·1
June	8	..	1·190	..	4·3	..	1-3·9
,,	9	..	1·370	..	4·3	..	1-3·1
		Total	16·814	..	69·6	..	1-4·1

* Two consecutive experiments.

From the figures given in the above table it is seen that the total excretion from the lungs was 16·8 grams, and from the kidneys 69·6 cc., giving a relation of 1—4·1, a difference of six points in the first place of decimals from the relation obtained from the above-quoted work on physiology. If in the same table we take the highest excretion from the lungs, 1·67 grams, the corresponding excretion from the kidney is 7·3 cc., the lowest from the lungs is 1·16 grams, and the corresponding kidney excretion 4·5 cc. The highest excretion from the kidney is 7·6 cc., and the corresponding excretion from the lung 1·5 grams; the lowest from the kidney is 4·3 cc., and the corresponding excretion from the lung 1·1 grams.

Thus it appears that within the limits imposed by the physical laws which govern the saturation of the atmosphere with moisture, the excretion of water from the lungs does vary on parallel lines with the excretion of water from the kidneys with a relation of 1—4·1 to 1—4·7, and things that increase the excretion of water from the kidneys will increase the excretion of water from the lungs within these limits.

I have also made similar experiments with opium, mercury, and nitrites, and find that when these increase the urine they at the same time increase the excretion of water from the lungs.

My research seems to show that Dr. Yavein's observation was correct and that an alkali which diminishes the water from the kidneys (see p. 187) so long as it increases (*but only so long*) the uric acid in the blood and urine, will at the same time diminish the excretion of water from the lungs to a corresponding extent.

We must now consider the probable cause of this parallelism of the two excretions.

In everyone from hour to hour and from day to day the excretion of water from the kidney varies in the reverse direction with the excretion of uric acid; and so constant is this law, that by controlling the excretion of uric acid I can control the water with a certainty little short of absolute. In clinical work, if the water is known from day to day, the uric acid, greater or less, can be calculated from it with considerable certainty (see *Lancet*, July, 1892, and elsewhere); and not only so, but all the important drugs (mercury, opium, salicylates, iodides, caffeine, &c.) which cause diuresis do, as I have shown, diminish the excretion of the uric acid at the time of the diuresis, or, as I put it, they cause a diuresis by clearing uric acid out of the blood and freeing the capillaries of the kidney, because the obstruction of the capillaries throughout the body varies directly with the amount of uric acid circulating in the blood (see *British Medical Journal*, February, 1889).

But in the uric acid headache and other conditions in which there is an excess of uric acid in the blood, not only is the urine scanty and the skin pale, cold and dry, but the saliva also is scanty, and it can be shown (*Brain*, 1893; and chapter x.) that the gastric juice, the bile and the intestinal juices are the same. We see there is reason to believe that the excretion of water from the lungs is correspondingly diminished. The explanation is simple, for the capillaries are all obstructed by uric acid in the blood (collæmia), and if the blood is now examined it will be found to contain an excess of water, both hæmoglobin and cells being relatively diminished. The corresponding obstruction of the capillaries of the skin can be demonstrated and its amount measured by anyone by means of the capillary dynamometer mentioned in chapter v.

Uric acid, therefore, which obstructs the capillaries throughout the entire systemic circulation and diminishes all the excretions, affects also the vessels of the lungs and diminishes the output of water to a corresponding extent.

What is the bearing of these facts on the pathology of asthma, a paroxysmal disturbance of function resembling at so many points migraine, epilepsy and Raynaud's disease, which are also paroxysmal?

I think it can be shown that migraine, epilepsy and Raynaud's disease are paroxysmal in relation to the fluctuations in the excretion of uric acid and the amount that is passing through the blood, migraine and epilepsy representing the effects of high blood pressure on the intracranial circulation, and Raynaud's disease the effects of

obstructed capillaries on the nutrition of the skin and extremities (chapter xi.).

Asthma appears to be paroxysmal in relation to similar fluctuations of uric acid; is it one of the effects of uric acid on the pulmonary circulation?

Let us consider one or two points in the anatomy and physiology of the lungs.

We have two circulations present: (1) that of the pulmonary artery in which there is comparatively low pressure, and (2) that of the bronchial arteries which come from the systemic circulation, in which there is much higher pressure; and we have these circulations enclosed in a cavity, the pressure in which varies greatly from moment to moment with respiration.

But if you diminish the atmospheric pressure on any vascular area of the body, its capillary vessels at once dilate (see Marey, "La Circulation du Sang," 1881, p. 444), and it seems obvious that most blood will stream into that area which has the highest blood pressure behind it, because it is the pressure in the arteries which drives the blood through the capillaries into the veins (see Marey, p. 321, *et seq.*). It follows that when atmospheric pressure is diminished in the thorax there will be more congestion in the bronchial circulation than in the pulmonary; and more congestion in the bronchial circulation, the higher the blood pressure in the systemic circulation of which it forms a part.

Here we have a tendency to hyperæmia and congestion in the lungs, which is probably most marked in the area of distribution of the bronchial arteries, which will increase with rising blood pressure and with anything that obstructs the free entry of air into the thorax, and so tends to diminish more than usually the atmospheric pressure during inspiration.

It is interesting to note that Marey (previous reference, p. 448) attributes in no small degree to the diminished pressure in which they have to work the ease with which the lungs become congested or inflamed.

I believe such a congestion or hyperæmia, affecting especially the bronchial circulation, may quite account for the retro-sternal pain, with slight increase of bronchial secretion and wheezing, which I have myself experienced in connection with excess of uric acid in the blood and the high blood pressure it produces, and a slight increase of this disturbance may easily account for the bronchial congestion of asthma.

May not something of this kind represent the internal factor in

the causation of a common cold, and explain its relation to dyspepsia, menstruation, &c., which so often upset the physiological balance, and bring an excess of uric acid through the blood, producing high blood pressure and, in the way just explained, hyperæmia or congestion in the area of the bronchial circulation in the thorax?

Is not this an indication of the causation of chronic bronchitis and its frequent association with chronic Bright's disease and high blood pressure in the declining years of life? Bronchitis also is common at the two ends of life, and in both we see excess of uric acid, excessive formation in children and excessive excretion in the old.

It is in the declining years of life that, owing to failing nutrition falling urea and diminishing acidity, we get a very large amount of uric acid dissolved and passing through the blood, and most in those who have taken most freely a highly nitrogenous diet in the previous twenty or thirty years.

The collæmia thus induced obstructs capillaries and raises blood pressure, and the further general failure of nutrition, chronic Bright's disease, and chronic bronchitis are secondary. It is little wonder that, as pointed out by the late Professor Humphry, a large proportion of those who attain great age are more or less strict vegetarians.

It seems probable that when once this bronchial hyperæmia has taken place the swelling of the mucous membrane may further obstruct the passage of air to the bronchi and alveoli on the distal side of the obstruction, and this will lead to continually increasing fluctuations in the pressure in the distal air passages with increasing hyperæmia and congestion, so that trouble increases and the hyperæmia only subsides after it has been relieved by a copious secretion of mucus or a general oozing of blood.

I do not think an affection of the bronchial area alone will account for the fluctuations in expired water which take place, and I believe that uric acid will affect the pulmonary vessels as well as the bronchial, and may possibly do this to the extent of greatly obstructing its vessels and rendering the whole lung anæmic, but this is probably a rare condition, though occurring perhaps in uræmia or other organic disease. The more common effect of collæmia and high blood pressure is congestion and hyperæmia in the area of distribution of the bronchial arteries, which, when slight and chronic, may lie at the root of chronic bronchitis or the onset of cold, but when more sudden and severe may produce an asthmatic paroxysm.

If asthma has this causation it will be made worse by anything that obstructs the capillaries and raises blood pressure, and better by anything that frees the capillaries and lowers blood pressure. It will also be made worse by anything obstructing the free entry of air into the thorax.

The most common cause of high blood pressure is uric acid in the blood, and this explains the relationship of asthma to gout and various other diseases.

The cause of the asthmatic attack in the early morning hours is its relation to the largest excretion of uric acid in the twenty-four hours and the change about 4 a.m. from a free circulation to an obstructed one (fig. 2). Asthma at this point parallels very closely the causation of angina.

During sleep the patient is generally in the recumbent position, and this raises the general arterial tension as compared with sitting or standing. (Marey, previous reference, p. 349). Hence a sufferer can sometimes sleep in a chair but not in a bed, though no doubt position also affects the action of the muscles of respiration.

I have mentioned the relationship of asthma to diet, and this is explained by its effects on the uric acid in the blood. Not a few of the minor premonitory symptoms of an attack are those of collæmia.

No one who understands the relationship of dyspepsia to migraine and epilepsy will have difficulty in understanding its relationship to asthma. In all cases, however, the relationship is a double one. Dyspepsia is partly a cause and partly an effect of collæmia and high blood pressure.

There can be no doubt that collæmia, when it obstructs the capillaries, may practically suspend entirely gastro-intestinal digestion and absorption, and allow putrefactive processes to take their place; in this way collæmia causes dyspepsia (see chapter x.).

But dyspepsia will cause or increase collæmia. Suppose there is no excess of uric acid in the blood, but that some indigestible substance upsets gastric digestion; the result is the more or less complete arrest of digestion and absorption, even if there is no vomiting, and this causes a fall in urea and in the acidity of the urine; the alkalinity of the blood is increased, and any uric acid within its reach is taken up in solution. Such is the usual causation of a "bilious attack," or uric acid storm. The high blood pressure resulting from the passage of the uric acid produces either headache or epilepsy, or (if the dyspepsia is chronic rather than acute) mental depression, and leads through chronic obstruction of metabolism

and combustion to that great general failure of nutrition which we call Bright's disease.

I believe the relationship of asthma to dyspepsia is precisely similar, and in some cases the cure of dyspepsia is the cure of asthma.

The relationship of asthma to gout is equally simple, and is shared by migraine, epilepsy and Raynaud's disease.

Asthma is due to uric acid in the blood, *i.e.*, to the high blood pressure it produces. When from any extraneous cause, a blow, a chill, local irritation, or rise of temperature, uric acid is precipitated on a joint, the blood is cleared of the excess it previously contained and the high blood pressure and asthma subside. It is told of Frederick the Great (*British Medical Journal*, 1888, vol. ii., p. 954) that he had a severe attack of dyspnœa followed next day by gout. It is added that he was very gouty and had an irascible temper, this last representing the effects of uric acid on the intracranial circulation as the dyspnœa represented its effect on the thoracic.

Phthisis and gout are sometimes said to be related (see *Medical Times and Gazette*, 1862, vol. i., p. 499, and *Deutsch. Archiv. f. klin. Med.*, Bd. 47, Hft. 5 and 6; also Sir Dyce Duckworth, "A Treatise on Gout," p. 172), and they certainly often occur in members of the same family. They alternate, just as asthma and gout do, and this was the opinion of the late Sir Andrew Clark, arrived at, as he himself told me, from personal experience (see also *British Medical Journal*, October, 1889).

Speaking of his own case, he said: "When I was a young man I had to choose between gout and phthisis, and I chose gout," evidently thinking that by eating a large amount of animal food he was cured of phthisis and got gout. His words impressed me because they raised in my mind the fear that in escaping gout I might invite phthisis. It was a discussion on diet with reference to my observations that led him to make the above statement.

There can be little doubt that he chose wisely, for though collæmia and high blood pressure eventually caused his death, he had lived for many years an active and useful life.

I believe the changes in the pulmonary circulation which uric acid produces may completely account for this antagonism between gout and phthisis. For while a man is eating largely of animal foods he will have high acidity, his blood will be pretty clear of uric acid, and his pulmonary circulation will be free, but he will have gout because he is storing and retaining large amounts of uric acid.

Let this man, however, meet with an accident which confines

him to bed for weeks or months, so that appetite, digestion and metabolism run down; with falling acidity the stored urate will pass in excess through his blood, his pulmonary circulation will be more or less markedly deficient and the bacilli will have their opportunity and may not neglect it. I consider such chronic collæmia a great danger for the lungs.

Of course it may be possible, even after the bacilli have obtained a foothold in the lungs, to destroy them by taking a large amount of animal food, which, as we have seen, keeps the blood free from uric acid, and makes the fires of life burn brightly.

Collæmia may also be kept up by dyspepsia and other gastric troubles, hence perhaps the origin of the dictum I have heard at lectures at Brompton Hospital with reference to the treatment of early phthisis, "Take care of the stomach, and the lungs will take care of themselves."

A similar explanation may also apply to the cases of acute phthisis following destruction of the mucous membrane of the stomach by corrosive fluids recorded by Dr. Soltau Fenwick (*British Medical Journal*, 1894, vol. i., p. 129).

Phthisis, like asthma, is often markedly worse in the spring of the year (see Dr. Barlow, *Lancet*, 1891, vol. ii., p. 285; also fig. 4), and iodides are supposed to be useful in cases in which there is a syphilitic taint, but if these drugs keep the blood free from uric acid (fig. 22) and thus allow a good circulation through the lungs, I should be prepared to find that they cure many cases unconnected with syphilis.*

If the observation of the late Sir A. Clark is correct, and can be thus explained, we should be able to escape phthisis and burn up the bacillus of tubercle, without having to reckon later on with the serious effects of collæmia and high blood pressure. There are many ways of clearing the blood of uric acid and stimulating the fires of life without introducing a large amount of uric acid in the food for future trouble. Sir A. Clark did not excrete all the uric acid introduced in meat, eggs, &c., and as age approached it returned into his blood, producing disastrous collæmia, high blood pressure and cerebral hæmorrhage. Again, fever (as in phthisis) may be Nature's attempt to burn up the invaders, and we should obviously help her endeavours by keeping the capillaries as free as possible from uric acid. If the progress of phthisis is thus depen-

* It is interesting to note also that iodides appear to be useful in actinomycosis (see *British Medical Journal*, 1894, vol. i., p. 61).

dent on the effects of uric acid on the circulation and combustion, we can easily understand the observation recorded by Dr. Barnes in the *Lancet*, 1894, vol. ii., p. 1266, that phthisis makes increased progress from the moment of parturition; it even appears, like migraine, epilepsy, asthma, and Raynaud's disease, to be slightly better during normal pregnancy.

Asthma occasionally alternates with epilepsy, and this is probably due to the fact that some third factor has for a time rendered the thoracic circulation more liable to be upset by collæmia and high blood pressure than the intracranial; any temporary interference with free inspiration might, as I have suggested, account for this (see also a case recorded in the *Lancet*, 1893, vol. i., p. 1383).

The relationship of asthma to eczema and skin diseases is probably simple, for I have pointed out (see chapter xi.) that not a few skin diseases represent merely the effects on its nutrition of vessels obstructed by uric acid; and I have taken this probability as my guide in the treatment of such skin diseases as come under my notice, with results which have often appeared to be very satisfactory.

We must remember that such skin lesions are produced in the vascular area, the deep layers of the skin, and hence may take several days to appear on the surface; meanwhile the collæmia which produced the asthma and the skin troubles may have disappeared, so that it may seem to alternate with the skin trouble when it is really contemporaneous.

The relationship of asthma to nasal irritation and obstruction may be that these tend to diminish the free inrush of air in inspiration, and thus lessen for a time atmospheric pressure in the chest, and so increase congestion in the bronchial area, other things, such as blood pressure, remaining the same.

Asthma is sometimes decidedly relieved by the use of compressed air ("Aerotherapeutics," Dr. C. T. Williams), which would from this point of view increase the inrush of air in inspiration and also diminish the congestion in the bronchial area, thus increasing the space available for the incoming air.

Hay asthma, cat asthma, &c., may in this way be due to the irritant action of small particles in producing nasal congestion and obstruction, with the concomitant action, in the case of hay asthma, of heat, which increases the alkalinity of the blood and the amount of uric acid it will contain.

In hay fever there seem to be two chief factors, (1) the presence of vegetation with its irritating pollen, as in the case of hay; (2) heat

or relative heat of a climate affecting probably uric acid collæmia and the circulation ; so that while natives of an elevated district may suffer, those who come there from lower and warmer districts obtain relative immunity from collæmia, and so find relief (see Solly, previous reference, p. 156).

A number of people with chronic gout, chronic collæmia, defective capillary circulation and high blood pressure suffer more or less constantly and severely from congestion of the naso-pharyngeal mucous membranes, frequent nasal obstruction, sneezing, paroxysmal sneezing, &c.

And when a person having such circulatory conditions and tendencies to nasal congestion is subjected to heat plus pollen dust, it is small wonder they develop more severe symptoms.

I have long believed such conditions could be relieved by the diet and drug treatment that removed collæmia and prevented the recurrent irritation of mucous membranes by urates, and in my cases I have given no special attention to the nasal symptoms, as all my interest centred in the circulation conditions and general effects of collæmia.

I consider that when an inflammation of the nose or pharynx follows on obvious exposure to cold it is of the nature of a uric acid irritation of the affected mucous membranes, but where (as in hay fever) it is the result of conditions of heat which cause collæmia, and of pollen irritation causing local congestion, it is rather of the nature of a local congestion in association with the defective circulation of collæmia.

In my own cases it has often appeared to me that both conditions were present, and in the pharynx we see the condition of chronic congestion so common in gouty or rheumatic (arthritic and collæmic) subjects.

The important point is that the proper treatment of collæmia and circulation conditions relieves the whole trouble, whether due to direct urate irritation or to high blood pressure or both; and I am glad to see my own experience in this matter has been shared by others, as Dr. J. Dunn, of Richmond, Va., U.S.A., who has a paper on "Uricacidæmia as the cause of Hay Fever and Asthma" in the *Virginia Medical Semi-monthly*, February 10, 1899, p. 630. In an interesting letter he tells me that he sees hay fever at all seasons of the year, though it goes by another name when hay is not in season. The treatment of which he records the success was diet alteration with a tonic, or an iodide.

Dust, even in ordinary asthma, will often account for the onset

of an attack, such as the dust of particular trades, fine particles of hay or straw, the dust of long railway journeys in dry weather, even the dust of unused rooms and old books. All these act in much the same way, producing nasal irritation and congestion, the bronchial trouble being secondary to the blocking of the upper respiratory passages thus brought about.

Bad air and deficient oxygen may act by increasing the alkalinity of the blood; deficient oxidation probably produces collæmia in this way; hence the headache of badly-ventilated theatres, and crowded rooms (see pp. 53 and 91).

Certain odours produce more or less nausea which will increase the alkalinity of the blood; and shock or fear have much the same effect, and so precipitate an attack of asthma: these last are well known to have a similar effect in chorea, Graves' disease, diabetes, and practically all collæmic troubles.

The drug most widely used in asthma is probably iodide of potassium, or the iodides: and it is interesting to find that they free the capillaries and lower blood pressure by clearing the blood of uric acid (see fig. 22).

The iodides probably relieve asthma by clearing the blood of uric acid and so reducing blood pressure and the resulting congestion in the area of the bronchial arteries; I have given in my paper on "The Iodides" * a figure to show the effect of Hair's asthma cure on the excretion of uric acid.

An experience of the value of iodide of potassium in asthmatic affections is recorded by Sir W. T. Gairdner in the *Lancet* (1901, vol. i., p. 1590).

Of the action of acids, morphine and the nitrites I have already spoken, showing that they, like the iodides, clear the blood of uric acid.

Bleeding will obviously reduce blood pressure in the systemic circulation, and tobacco and lobelia are cardiac and muscular depressants, and probably lower blood pressure partly in this way (see also p. 345).

Antipyrin, I believe, acts as an acid, freeing the capillaries by clearing the blood of uric acid; but it may also act to some extent like the cardiac depressants, and it seems probable that the fumes of sulphurous acid or of nitre paper diminish the alkalinity of the blood, and so tend to clear it, while the smoke of tobacco and other burning vegetable substances contains acids of similar action.

I think there is no practical doubt that asthma results from the

* See *Medico-Chirurgical Transactions*, 1893, vol. lxxvi., p. 113.

action of obstructed capillaries and high blood pressure on the thoracic circulation, though, as in the parallel case of the intracranial circulation, certain local or general conditions may affect to an important extent the result in any given case.

I have also no doubt that the circulatory changes are generally due to uric acid in the blood (see "International Clinics," vol. iii., third series).

If these deductions are correct the indications for treatment are moderately clear and distinct, namely: (1) To reduce and keep down blood pressure; (2) to clear and keep clear the upper respiratory passages, so that the atmospheric pressure in the chest shall not be unduly reduced during inspiration.

Blood pressure may be reduced either by freeing the capillaries or weakening the heart; the iodides, morphine, calomel, or the salicylates free the capillaries, by clearing the blood of uric acid, while acids and probably the inhalation of acid fumes act in the same way.

Or it may be kept down by reducing the amount of uric acid directly introduced or formed in the body, by alteration of diet, and it was the relief of asthma by diet given for headache that first directed my attention to it.

Blood pressure may also be kept down by stimulating metabolism where this is possible; for, as metabolism goes up, urea and acidity rise, and the blood is kept clear of uric acid (see chapter iv.). This may be done by regular graduated exercise, avoiding carefully the fatigue point, or by massage to improve the circulation and metabolism in the muscles and skin. Neither of these treatments, however, diminish the amount of uric acid in the body; on the contrary, they increase it, while they keep the blood clear, and when further stimulation of metabolism is no longer possible, as in old age, severe collæmia supervenes (see following chapter).

For this reason I consider that diet which permanently reduces the amount of urate in the body is better treatment than stimulation of metabolism, which, while it clears the blood, causes urate to be stored. Iodides or other drugs which clear the blood of uric acid produce the same result; and if they are followed by a course of salicylates the troublesome rebound may to some extent be avoided.

The condition of the upper respiratory passages is generally a matter for the surgeon; but as an excess of uric acid in the blood may, by affecting their circulation, tend to produce or keep up congestion of the nasal and the other mucous membranes, I should be

inclined, where such local troubles are slight and merely congestive, to give diet a careful trial before resorting to surgery.

A most interesting paper by T. H. Buckler, of Paris, in *The American Journal of Medical Sciences*, July to October, 1882, p. 347, bears the title "Rheumatic leucoinitis of the pulmonary air tubes, and relating also to the pneumonia and solid engorgement supervening thereon."

Apparently "leucoinitis" refers to the inflammation of the white fibrous tissues of the air tubes, which, according to the author, are the chief seat of the disease.

He sees no reason to believe that the white fibrous tissues of the air tubes are any more exempt from disease than the fibrous tissues of other parts.

In a case of uræmia where I relieved coma and head pain by bleeding, acute bronchitis came on next day and soon caused death, and I note a somewhat similar result in a case described by Mr. L. A. Ffancis in the *British Medical Journal*, 1902, vol. i., p. 71. Here puerperal eclampsia was treated by morphine, and acute bronchitis supervened. Was this an acute gout of the respiratory passages due to retention by morphine; and in my case was it due to retention by rise of temperature and acidity after venesection? If so, a course of salicylate after the morphine or the venesection might have saved life.

The signs of this inflammation of the fibrous tissues of the air tubes (fibro-bronchitis) are: fever, cough (which is dry, often paroxysmal), absence of signs of catarrh in the chest. Such bronchitic signs may alternate with a rheumatic arthritis of the shoulder, or other neighbouring joints, and the fibrous tissues of the endocardium or pericardium may be affected.

He calls this trouble rheumatism, but what he really means is a gout of the fibrous tissues (though gout is rheumatism, and rheumatism is gout, see chapter xv.), and he refers to an article by Dr. Black, in the *Edinburgh Medical Journal* of 1854, who found crystalline particles of uric acid and urate of soda in the said white fibrous tissues.

After the air tubes have been affected in this way, the lung round or between them becomes pneumonic and solidified, and tends to remain persistently in that condition (rheumatic pneumonia).

Such pneumonia may change from place to place (metastasis), going from one bronchus to another, or from one lung to another, and affecting the heart on the way.

Professor May records, in a paper in the *Philadelphia Medical*

Journal, March 18, 1899, that he found a personal history of rheumatism in 12 out of 80 cases of acute pneumonia.

Dr. Buckler's great point about these rheumatic inflammations is that they yield at once to treatment with salicylate of soda, but if the rheumatic element is not treated they are extremely intractable.

(We may recall my remarks about the treatment of catarrh and bronchitis by solvents and their position in the precipitation group of uric acid diseases).

Tubercle may find a nidus in the pneumonia so produced, and the resulting phthisis may eventually leave no trace of the rheumatic inflammation in which it origniated.

The cause of this inflammation is generally exposure to cold or damp, or both, such as sleeping in wet clothing, &c.

The author believes the salicylate acts by dissolving uric acid out of the fibrous tissues, and it is most interesting that he thinks salicylates will not act well when the urine is alkaline, and finds the best indication for their successful use is an acid urine turbid with urates which clears on adding liq. ammoniæ. The other drugs he uses are phosphate of ammonium (which he regards as a very good solvent of uric acid), and fresh lemon juice, the latter to be given when there are phosphates in the urine.

He considers that a London fog with low temperature may cause such rheumatic bronchitis and pneumonia, and these may produce serious and fatal results if the rheumatism is not treated.

The cough is dry and paroxysmal, and if such a cough exists without a long uvula and with few or no chest signs, the disease is rheumatic fibro-bronchitis.

Curiously enough he also says that this rheumatic inflammation of white fibrous tissues is never attended by pain, which is not only in marked contrast with the effects of gout in other fibrous tissues, but differs very much from my own experiences of gout of the trachea and bronchi, to be related in reference to fig. 74.

Such is an outline of this interesting paper.

I do not doubt that uric acid causes inflammation of all these fibrous tissues, of the digestive and respiratory tubes, of the pharynx and œsophagus, and of the nose, larynx, trachea, bronchi, lungs and pleuræ, and I have had some of them a good many times.

The trouble in the nose and pharynx causes burning and discomfort rather than pain; in the œsophagus there is pain with local tenderness, as of a bruise, as each bolus of food goes down. In the larynx there is a feeling as of a ring of dryness with a certain amount of burning, and as this passes down and involves the glottis

there is hoarseness. We have here a local precipitation which must be treated by solvents.

In the trachea there is similar dryness and burning, but if the inflammation is at all acute there is burning pain as if the structures were red hot, and they feel as if badly bruised and most tender to cough.

The whole of these troubles are the result of exposure to cold, especially after fatigue and perspiration; for instance exposure to cold wind after getting one's beard cut a little too short will start a pharyngitis.

Those who write on pharyngitis give cold as a cause, but do not explain its action. It will, however, be evident that it acts here just as in arthritis and lumbago and a host of other irritations of fibrous tissues by uric acid. Thus cold acts on a surface containing fibrous tissue the blood coming to which is rich in urate; the result is that some of the urate is retained locally and gives rise to irritation and inflammation, and swallowing or inhaling acids will do the same thing. The tissues are now a uric acid filter and the irritation will continue so long as the blood supplies uric acid. The moment solvents (alkalies and salicylates) place the blood in the position to take up uric acid from the filter, the urates are removed and the troubles in these and all other fibrous tissues subside.

There are two ways of meeting the trouble, (1) avoiding cold, which is quite impossible in this climate; (2) keeping the blood free from excess of uric acid, which eighteen to twenty-four months on a uric-acid-free diet will do; and then (in my own experience and that of many others) the catarrh ceases just as do the signs of gout and rheumatism in other tissues. There is nothing occult about it; if you understand urate irritation in one fibrous tissue you understand it in all. The prevention is the prevention of collæmia; the cure is the solution of a precipitation which cold, acids, a microbe, or all acting together, have produced from the collæmia.

For some interesting points and facts as to the connection of diseases of the nose and throat with gout, rheumatism and asthma, and for the record of a case where podagra and pharyngitis alternated, see the Lettsomian Lectures by Dr. de Havilland Hall (*British Medical Journal*, 1897, vol. i., p. 449). In my own case it will be seen in the description of fig. 74 that tracheo-bronchitis alternated with gout of the intestines.

I hear from Dr. Mackie of Nottingham, that he has noted an almost constant connection between catarrhal conditions of throat and ear, adenoids, &c., and the uric acid diathesis, and has read two

papers on the subject before the Medical Society of Nottingham. He says, "I scarcely see a case of adenoids, say in a child, but where there is an arthritic or migrainous parentage," and it is obvious that such conditions may easily result from recurrent uratic irritation (see also cases of tonsillitis and enlarged cervical glands recorded in chapter xvi.).

When acute, the inflammation of the nose, pharynx and respiratory passages ends by the discharge of yellow pus, and no doubt the œsophagus does the same, this being completely identical with what I shall describe as gout of the intestines, which also, as we shall see in my description of the circumstances and symptoms attending fig. 74, ends in the discharge of muco-pus from the bowel.

In the same way the pleura may be affected either by extension of a gouty pneumonia or by more direct precipitation of urates on a given point of lung surface.

Some most interesting cases of pleurisy unmistakably due to cold, for they occurred in man after man on exposure to cold while warm and perspiring and always on the side exposed, are mentioned by Dr. G. R. Murray in the *Lancet* (1902, vol. i., p. 1447). These cases were certainly due to rheumatism—that is, to uric acid, and this was precipitated on the pleura by the cold, just as it is on other fibrous tissues in diseases of the local group (see p. 134).

They are all extremely amenable to treatment by salicylates, and their most severe symptoms subside within an hour or two after taking a dose; but as is pointed out by Dr. Buckler, there is one condition which interferes with their action, namely, low acidity of the urine which goes with high alkalinity of the blood. This hinders salicylates from acting as solvents of uric acid and so prevents their relieving these troubles.

Dr. Buckler's reference to the possibility of tubercle being engrafted on such a gouty inflammation of fibrous tissues is most interesting; do we get here a possible explanation of the marked and well-known lowering of the temperature of phthisis by salicylate of soda? Is phthisis at certain stages an infective tubercular process plus a gouty inflammation of neighbouring fibrous tissues?

I have considerable confidence that every so-called common cold originates somewhat in this way. There is first an irritation of an exposed surface, as the nose or pharynx, by cold, dust, pollen, or other irritant particles, possibly by the microbes of catarrh themselves, and on this supervenes, owing to the presence of uric acid in the blood, a gout of the neighbouring fibrous tissues. The gout

and the catarrh microbes spread through these, but the catarrh will not spread without the gout. Hence salicylate of soda cuts short the process in a few hours. Those who have not excess of uric acid do not suffer from such catarrhal and gouty inflammations. The observed influence of milk diet in preventing and relieving bronchitis should be noted (Semmola).

A uric-acid-free diet greatly diminishes liability to cold, and uric acid solvents repel its attacks and render the soil unfavourable for the spread of the microbes.

This is also the case when the blood is relatively free from uric acid, as in good condition or training, which explains the observation of Dr. O. Clayton Jones in the *Lancet*, 1902, vol. i., p. 195, "Men in good condition seldom catch cold. It is a rare thing for a rowing crew to catch cold, although the coxswain and coach often suffer."

The crew are (like the men on Ben Nevis) in a condition of stimulation and free from collæmia, but retaining uric acid in their livers; when training is over they run down, and the said uric acid comes into their blood, when they may get a cold, and a bad one.

This explains the deadly effect of exposure to cold when hot and fatigued, for heat and fatigue bring uric acid into the blood; the cold drives some of this into the local fibrous tissues (nose, pharynx, larynx), producing a uric acid filter where the microbes settle and flourish. A solvent promptly administered will remove this (see p. 174), when the microbes are left stranded.

Does phthisis, as Dr. Buckler partly suggests, originate in the same way, the tubercle bacillus and the gouty "leucoinitis" working together and helping each other? If so, we have a most interesting and useful explanation of the connection between gout and phthisis, which will also explain several points already referred to in this chapter, such as the relation between phthisis and spring-time, when there is in most people an excess of uric acid passing through the blood, its relation to dyspepsia and gastric troubles, which bring about a similar result (collæmia), and to pregnancy and parturition.

This also explains the late Sir A. Clark's experience, for though he cured his phthisis and got gout in middle life and collæmia later on, the first effect of his liberal diet was (as I have said with regard to the cure of gouty arthritis by a pure meat diet chapter xv.), that he was stimulated by the diet and his blood was for a time kept clear, during which time the combined activities of gouty fibrosis and tuberculosis ceased.

Do we not here also get insight into the pathology of that disease in which the late Sir A. Clark himself took so great an interest, namely, fibroid phthisis? May this not be a condition in which the gouty fibrosis outruns the tubercle and eventually almost replaces it?

A bracing place or mountain climate acts like stimulating diet, and keeps the blood clear of uric acid for the time, hence the microbe of catarrh can get no foothold, and the well known effect of such a climate in phthisis has most probably an identical chain of causation.

Be this as it may, I can answer for it that a common cold can at once be cut short by one or two fractions of a grain of calomel (gr. ¼ to ½ ter) followed by salicylate of soda (gr. xv. ter vel quater) for four or five days.

In my own troubles the only point is whether they are bad enough to require treatment, but there is never any doubt that I can cure them with salicylate. The purpose of the above calomel is to partly clear the blood of uric acid and stimulate nutrition and thus produce a condition favourable for the best action of salicylates (see also remarks on figs. 71 and 74).

The whole of these gouty and catarrhal inflammations of fibrous tissues have one important characteristic (noted also by Dr. Buckler): they tend to fly from place to place, one getting better as the other gets worse; they have another characteristic which they share with other and better known gouty inflammations, that when once a fibrous tissue has been affected the gout tends to return, or there is possibly left in these fibrous tissues a small residue of uric acid (such as that found by Dr. Black, quoted in Dr. Buckler's paper) which tends to attract more uric acid. This reveals the great importance of administering the salicylate for a sufficient length of time to clear out *all* the uric acid from the affected fibrous tissues, a principle somewhat blindly acted upon in the treatment of acute rheumatism, but not even then perhaps to a sufficient extent.

Before leaving this aspect of the causation of phthisis, I would call attention to the case of M. J., narrated in chapter xvi., where the administration of an acid and some strychnia produced an arthritis of a neighbouring joint (the shoulder, just as in Dr. Buckler's cases), and also probably an endocarditis of the mitral valve. Salicylate of soda relieved these troubles and brought down the temperature; I may say also that M. J. came of a decidedly gouty family.

We may gather some useful indications from the above pathology of phthisis, which, if well founded, may help us greatly in treatment.

With regard to catarrh, I am of opinion that those who live on a milk or uric-acid-free diet, are much less liable to it than meat eaters, suffer less severely when they get it, and in old age also are less liable to chronic bronchitis.

In phthisis we may have to deal with two similar factors, a gouty inflammation kept going by excess of uric acid in the blood, and a microbe which lives by its help. I was much interested in a letter from their correspondent at Rome which appeared in the *Lancet*, 1897, vol. i., p. 214, where it was mentioned that certain pathologists in America and Italy incline to regard phthisis as a disease of nutrition rather than of infection. I wrote a letter mentioning some of the above points which appeared in the same journal, p. 275.

The obvious indication is to clear the blood of uric acid and to burn up the microbe, which may be done by a stimulating diet, which keeps the blood clear of uric acid for a time. There is a better way still, namely, first to stop the gouty inflammation by a course of salicylate, and then to stimulate nutrition with a sufficiently nitrogenous, but entirely uric-acid-free, diet, with tonics freely given.

We shall thus keep the body clear of uric acid, and in destroying the microbe we shall not create a store of uric acid which may return into the blood at some future time, and in partnership with the microbe produce a relapse.

I have been interested in the writings of Professor Mays, of Philadelphia, on the neurotic origin of pulmonary consumption and its treatment by strychnine,* for I am not unmindful that migraine was called a neurosis, until it was found to be due to poisoning by uric acid, and the neurotic element in phthisis may thus simply represent its relationship to gout. Be this as it may, the treatment suggested by Professor Mays seems to me one extremely likely to go to the root of the matter if slightly modified.

This treatment consists of administering increasing doses of strychnia, beginning with $\frac{1}{30}$ grain four times a day, and increasing week by week up to $\frac{1}{12}$, or even $\frac{1}{8}$ grain four times a day, always, however, stopping short of the production of restlessness, twitchings, or other toxic symptoms. The rest of the treatment consists of feeding the patient on a highly nitrogenous diet of egg albumen, and this part I have modified by substituting the albumen of milk, cheese and bread, which introduce no uric acid or xanthin.

* *New York Medical Journal*, Feb. 15, 1896, and *American Medico-Surgical Bulletin*, May 9, 1896, also article in *Journal of Nervous and Mental Diseases*, November, 1896.

I have applied this treatment to several cases recently under my care, generally after a course of salicylates, and (as far as one can judge from a few cases) with results promising well for the future. At a meeting of the Æsculapian Society, with the object of suggesting the use of similar treatment by others, I showed one of these cases where marked disease at the right apex with anorexia, high and irregular temperature, night sweats and wasting, slowly and steadily cleared up on the treatment, whether post or propter.

I quite agree with the fresh-air and feeding-up treatment in cases of phthisis, with or without the doses of strychnine; but in my cases I always try to obtain the required nitrogen from uric-acid-free sources, and believe that I thereby obviate some of the danger of relapse.

On a uric-acid-free diet the danger of such relapse will be greatly lessened, while necessary stimulation can be obtained from strychnine and acid foods, fresh air and graduated cold bathing.

Similar stimulation can be produced by tonics, diet, uric acid or urea; all act in the same way and stimulate combustion by clearing the blood of the uric acid which is slowing combustion. The action of tonics is well known, they act by clearing the blood of uric acid. Hence everything that clears the blood of uric acid is a tonic, and every rise of urea is thus a tonic. Uric acid, as we know, clears itself out of the blood *pro tem.*, and meat extracts and juices, cod-liver oil and snakes' dung, &c., are the forms in which it is used. Cod-liver oil is an extract of liver, and some prefer to give liver extract freed from oil, only containing the uric acid and nitrogenous extractives.

All these uric acid compounds suffer from the defect that they are stimulants to-day, because they clear the blood of uric acid, and depressants to-morrow because they then return according to the supply of solvents in the form of uric acid, which causes collæmia and depression.

Urea is not open to this objection. It stimulates to-day because it raises acidity (diminishes the alkalinity of the blood), clears the blood of uric acid and improves combustion. But it is eliminated probably almost as fast as introduced, and there is no subsequent depression except what is due to the retained uric acid, which is the effect of all tonics and stimulants, mineral, vegetable or animal. When you use uric acid itself, you not only get this rebound, but are adding to the amount of uric acid in the body and to the subsequent depression which results.

I am, therefore, watching with interest the use of urea in tuber-

culosis, as described by Mr. A. H. Buck, Dr. Harper and others (*Practitioner*, July, 1901, and the *Lancet*, 1901, vol. ii., p. 1567). I have made some experiments with it which show that it raises the acidity of the urine, and acts as a stimulant in the same way as all the above-named substances. But for want of space I would give a curve to show this. If you produce gout you cure tuberculosis, for gout coincides with stimulated metabolism, tuberculosis with collæmia and depression.

A drug which produces similar effects to these, and which, when it clears the blood of uric acid, causes the fires of life to burn up brightly and destroy the invading microbes, is opium. But I think that though this drug has a considerable reputation in the prevention and treatment of phthisis, it has never as yet been used to the full extent of its power. It may be interesting to remember that opium as a preventive for phthisis has the powerful recommendation of such an acute observer as De Quincey. His dose of the drug reached the enormous extent of more than 300 grains a day, but between this dose and that of the pharmacopœia, I think it is possible to do more in the prevention and cure of phthisis than has as yet been systematically attempted. We have now what De Quincey had not, a drug (salicylic acid) which will enable us when we have produced the desired effects, to reduce the dose of opium or leave it off entirely.

Another instance of the same thing is probably seen in the occasional favourable action of mercury in cases of phthisis. I am of opinion that it not infrequently benefits others besides those in which there is a specific history.

A substance acting in the same way by raising acidity and clearing the blood of uric acid is sugar, the use of which in phthisis is mentioned in the *British Medical Journal*, Epitome, vol. i., 1905, p. 32.

Practically every substance which clears the blood of uric acid may do good in phthisis, and full diet and fresh air produce the same results for the same reasons.

Vegetarians, I believe, consider they have relative immunity from colds and influenza, and my experiences certainly favour their contention; I believe if they abstained not only from meat, but from eggs, pulses, tea and coffee, their immunity would be practically absolute.

This is a matter of wide importance, for those liable to catarrh from slight causes must avoid draughts and will only too often keep all their windows shut, thus existing in close or pre-breathed air, and

adding another important pre-disposing or exciting cause of phthisis to that which they already suffer from in liability to catarrh.

Persons free from introduced uric acid, and who excrete regularly day by day all that they form, are, I believe, free from all forms of rheumatism, from asthma, bronchitis, catarrh and, so far as I know, from influenza.

I believe, though it is difficult to prove, that they have considerable immunity from all the exanthemata, and also from pneumonia.

Doubtless in all cases the immunity is much greater in those who begin early in life. I myself began much too late. Once there is chronic catarrh, gout or rheumatism, immunity takes longer to acquire and is less perfect.

We have seen it proved that uric acid controls the capillary circulation, nutrition, metabolism, and combustion of the whole body, *e.g.*, in headache, mental depression and fatigue; we have yet to see that it controls digestion and the quality of the blood.

If the microbes of contagious diseases are raining equally on two men, the one with blood like sour claret, a capillary circulation giving a capillary reflux of 10 or 12, a pale fat-laden heart labouring to keep up a blood pressure of 160 by a pulse rate of 80—90 in the effort to force the capillary obstruction, the other with blood of magnificent colour, a capillary reflux of 4 or 5, a well-nourished heart which keeps up a normal blood pressure at a normal rate, muscles of natural colour and firmness, and tissues free from excess of waste products which are removed as fast as formed; can we doubt that in the one case the microbes will thrive in the pathological sewage farm on which they fall, while in the other they are burnt up, furnishing a few tiny atoms of an albuminous material which the brilliant combustion of the healthy organism can turn to its own profit.

Carbuncle is probably a local instance of the same thing, its relationship to gout being merely a relation to collæmia, and in the case of diabetes to collæmia and its result, defective combustion of sugar. Given a condition of collæmia, with its slow circulation and waste-sodden tissues, given a small surface abrasion to admit the microbe and you have all the conditions for carbuncle. The only favourable treatment is that which most quickly clears the blood of uric acid and allows circulation, nutrition, and removal of waste products to proceed.

Here we have in epitome, the pathology of catarrh, influenza, &c., probably also of malaria, pneumonia, tubercle and the exanthemata; in all there is a predisposing cause—collæmia—in all a microbe which takes advantage of the favouring conditions.

Persons who have not this magnificent combustion and consequent immunity from catarrh, can obtain it for a time by means of a drug in a way and to an extent which is remarkable, and throws a light on the causation of some of these diseases.

Let an individual of the collæmic catarrhal and rheumatic type who cannot expose his nose, larynx, trachea, or bronchi to the night air, or his neck or shoulders, or lumbar regions, to a draught without the most painful effects, let such a man take some 40 to 60 grains of salicylate of soda, or some 30 to 40 grains of salicylic acid or aspirin, and then let him run the same risk. He will find himself unhurt; no exposure, no snow-wet feet, nor lack of warmth will injure him or produce the common consequences.

Reversing the experiment, let him now try the effect of heat, a hot room in summer, or a Turkish bath. Pains, aches and catarrh will return with redoubled violence.

This transformation scene is merely a question of the solubility of uric acid in the blood, see p. 45 and fig. 71.

This is a demonstration that catarrh of any mucous membrane, respiratory or intestinal, represents the precipitation of a certain quantity of uric acid into its fibrous tissues, in which it remains (though probably still in colloid form as in the blood) and produces irritation.

Cold has the effect of making uric acid less soluble in the fluids of certain tissues to which it is applied; but when salicylates are in the blood with the urates, cold has the effect of increasing rather than diminishing their solubility, so that cold + salicylates does no harm, and instead of increasing a local irritation by urates, tends to remove them in solution and diminish it.

Salicylate + cold increases the excretion of uric acid in the urine and the number of granules in the blood; salicylate + heat, and especially + perspiration, does not increase the uric acid in the urine or the granules in the blood; if anything it diminishes them.

A cold, then, is a uratic irritation of the fibrous tissues of the mucous membrane concerned, and exposure can do no harm where there is no uric acid to be precipitated on the exposed part; nor when acting with a salicylate and aiding the solubility instead of precipitating uric acid.

There is much interest in a case of rhinitis excited by sulphurous acid (see *British Medical Journal*, 1899, vol. i., p. 1568) or the fatal case of bronchitis following inhalation of sulphur fumes, recorded in the same Journal (1899, vol. i., p. 1260).

In both I doubt whether the acid fumes would have done much

harm had there been no uric acid for them to precipitate on the mucous membrane, whose alkalinity they affected; I think prompt administration of salicylates would have done more than anything else to relieve, while in the bronchitis case (a man aged 59 and subject to asthma) they might have saved life.

I have no doubt that the catarrh produced by chlorides and iodides is simply an irritation of the fibrous tissues by precipitated uric acid, and this can be relieved by anything that removes the uric acid; either alkalies or salicylates.

The skin troubles produced by iodides and probably those by bromides have identical causation. The iodide is given to clear the blood of uric acid, and it causes irritation in the nose or skin or both by precipitating uric acid. The effect is antagonised or prevented by solvents such as alkalies or salicylates. This pathology also accounts for the terrible skin troubles in Bright's disease when iodides are given, for here the amount of uric acid in the blood is large and it is driven into a portion of the skin (see chap. xii.).

These, however, are single instances of a general law: "all troubles produced by precipitants are relieved by solvents; all troubles produced by solvents are relieved by precipitants." There are but two kinds of uric acid disease—gout and collæmia (see p. 134).

In this chapter we deal with one of each class; asthma is a collæmic disease relieved by precipitants; bronchitis is a precipitation relieved by solvents; what makes the one group better makes the other worse; what relieves the one produces the other; diet alone cures both.

In all forms of catarrh I have the utmost confidence in the salicylates, and in pneumonia I believe there is no better drug: but as they are powerful for good or evil, I shall state shortly the rules I have found necessary.

In all such cases salicylates are contraindicated by dyspnœa with marked cyanosis, by much perspiration, by gastro-intestinal irritation or vomiting, and by morbus cordis as a complication.

Briefly, they do well in early cases with rising temperature and before dyspnœa and cyanosis are marked.

While under their influence the patient must be kept cool, even if only covered with a single sheet.

As with rheumatism those who are taking salicylates are immune to cold, and no exposure, local or general, will harm them; not because there is no uric acid in the blood (collæmia), but because it is in such good solution in combination with the

solvent salicylate that it cannot be precipitated locally to cause either gout, rheumatism or catarrh. Both rheum and rheumatism have a common etiology and pathology; both are in part results of local cold and may be in part results of microbic action; but uric acid is the important factor in both, and if it is removed by solvents or kept out by diet neither cold nor microbe can do harm.

The fact that salicylates prevent catarrh as well as rheumatism is another indication of the etiology of the former.

If there is vomiting, either apart from or as the result of the drug, it must either be given up entirely or administered by rectum, or rubbed on the skin as salicylate of methyl, as is sometimes done in acute rheumatism.

Diet must contain some fish or egg, and some wine to keep up the acidity.

If other drugs are given with the salicylates they must be acids or salts of the mineral acids, not alkalies or alkaline salts on any account.

Salicylates should be given in a dose of 60—90 grs. per day for an adult or 30 to 50 grs. for a child; say salicylate of soda with sp. am. aromat. or nux vom. or salicylate of ammonia, and a carminative, as peppermint, ginger, or Inf. Gent. Co. gr. x. every four hours for an adult, the first two or three doses being at shorter intervals; or salicylic acid may be given as advised by De Becker for pneumonia (see Epitome of *British Medical Journal*, 1898, vol. i., p. 87) in doses of 30—40 grs. for a child, or 60—100 grs. for an adult in the twenty-four hours.

He advises small doses every hour or two hours, the acid dissolved in hot water and mixed with jam, honey, or diluted milk.

I do not think such frequent doses are necessary provided the proper quantity is given in the twenty-four hours, and if the doses are frequent at first so as to get up the power of the drug quickly as in acute rheumatism. In these respiratory diseases this is most important, for we must prevent dyspnœa and cyanosis, which create conditions unfavourable to the action of the salicylates. For adults the acid can be given in cachets; for children solution in hot water and milk is better, and it should always, if possible, be given after food, as this dilutes the irritant acid in the stomach and prevents irritation, nausea, and vomiting, with failure of absorption and control.

These drugs are certainly powerful for harm as well as good, and may cause severe collæmia with high blood pressure. This, acting with the block in the pulmonary circulation, causes rapid dilatation

of the heart and collapse, with a sudden and severe fall of temperature, though with proper care this should never occur.

Captain W. E. Beyts tells me he has got many good results in pneumonia by a modification of the above treatment; he not only gives salicylates internally but applies them freely to the surface of the chest as an ointment (containing sodii salicyl. gr. xx. to gr. xxx., to ʒ i. of vaseline) with an icebag, or cold in other form, over that.

In causation of pneumonia it is interesting to remember how often this trouble affects the seats of old lesions or follows a local injury, thus resembling all uric acid irritations of fibrous tissues. I remember seeing a man who had quite a definite lobar pneumonia in one apex (I think the left) which resolved in the ordinary way, the crisis on the seventh day. This man gave a history of having had a previous pneumonic attack affecting the same spot, and in this instance it followed closely on an injury by a blow from the shaft of a hansom cab. In my own experience I have not been able to distinguish between a pneumonia due to one cause and that due to another, nor have I seen any case of which it could be said, as it can be of pyæmia, that it was due to a microbe and could not be affected by salicylates. So far as I know, all cases seen early and treated properly by salicylates, or other solvents of uric acid, appear to do well with this treatment.

My experience shows that if the salicylates are given with knowledge of the above facts, they will give as good results in these diseases as in acute rheumatism. Almost the same precautions must be adopted, though the presence of dyspnœa is an additional hindrance to their best action, and necessitates further precautions in the case of chest trouble.

We shall understand, considering the causation of delirium as given on p. 322, how salicylates sometimes cause these conditions, for if the heart is weak or merely debilitated as in anæmia, the salicylate by causing collæmia may overpower it in this way and the resulting fall of blood pressure may in some people give rise to delirium. I have had several cases where it was easy to demonstrate that with the delirium went heart failure and subnormal blood pressure, though there was collæmia and the capillary reflux was slow.

The alternative treatment by alkali (which also produces good results, and is not contraindicated by dyspnœa and cyanosis) is to give sodii bicarb. to get the urine alkaline and keep it so until the temperature is normal, in three or four days. Then stop the alkali

and give a little belladonna and a carminative to diminish secretion and complete the cure. The temperature under alkali often reaches normal in a few days, but not so quickly as under salicylate, for the salicylate is helped by the fever to dissolve and eliminate uric acid, while the alkali must overcome the fever and its high acidity before it can act. Hence the importance of giving alkali freely at first to alkalise the urine. As the acidity of the urine in an adult is from the equivalent of 50 to 70 grs. of oxalic acid a day, no dose of alkali less than 50 to 70 grs. in the twenty-four hours is of any use, and considerably more may be needed.

In some of these cases of bronchitis it is clear that if there are any microbes they are unimportant. In many it is evident that the *rôle* of the microbe is to precipitate uric acid and to flourish in that precipitation ; clinical evidence becomes daily stronger that by keeping out the uric acid factor we prevent, and by sweeping it out with solvents we cure.

To be as nearly as possible free from excess of uric acid means a condition in which neither cold nor microbe, nor the two combined, can produce a local gout of the fibrous tissues of the respiratory mucous membrane, and this explains the observed immunity of those who live on a uric-acid-free diet. To be free from the attacks of these and other microbes it is advisable to be well nourished as well as free from excess of uric acid.

Asthma is a collæmic disease, to be treated and relieved by precipitants, but it also can be prevented by uric-acid-free diet.

CHAPTER X.

Dyspepsia and Gout of the Intestines.

In the uric acid headache, when pain is severe and mental and bodily exertion almost impossible, when skin and extremities are cold and urine scanty, there is good reason to believe that the circulation is equally defective in the glands and mucous membranes of the digestive system.

For the saliva is obviously scanty, and there are well-known facts which render it probable that gastro-intestinal digestion is almost at a standstill. The cases mentioned in chapter vii. must, I think, go towards proving that this is so in some epileptic fits; and it is common experience with those who see much of migraine and similar "bilious attacks" that food may be vomited after several hours sojourn in the stomach in a totally undigested condition. I suggest that this is due to the defective circulation in the glands and mucous membranes concerned, produced by excess of uric acid in the blood, and that a bilious attack is a mixture of dyspepsia and collæmia, a vicious circle in which the one first on the scene produces the other. Dyspepsia may be first and will produce collæmia; or collæmia, due to such a cause as fatigue, for instance, will produce dyspepsia.

A point bearing on this pathology is recorded in a letter in the *Lancet*, 1898, vol. ii., p. 1240, over the initials "G. C. L.," and appears to be a personal experience.

He has signs of a dilated stomach which come especially when he is "headachy" and which he connects with "neurasthenia."

He gets the same if he takes too much fluid, especially with meals.

For "headachy" I think we may read collæmic defective capillary circulation and high blood pressure causing headache.

These conditions in the stomach produce defective secretion, digestion and absorption, possibly also defective tone of the stomach muscles. The rest is mechanical.

In the *British Medical Journal*, vol. i., p. 345, is a lecture by Dr. H. A. McCallum on "Visceroptosis," in which he points out that the debility which leads to displacement of certain abdominal and pelvic organs is in many cases but a sign or symptom of neurasthenia. This has specially interested me because I have long known that more or less temporary dilatation of the stomach is very constant in conditions of collæmia, and others have pointed out that the dilatation of the stomach increases or diminishes with the severity of the collæmia. I have noticed that in a considerable number of such cases the right kidney is apt to be unusually movable and can often be felt; but whether the stomach has any action in dragging down the kidney or whether the kidney has any effect in displacing the stomach I am not able to say. I can only answer for it that the two conditions are frequently associated. Again, conditions of chronic collæmia, producing almost universal deficiency of nutrition, must no doubt result in debility of all the muscle structures, and among others the muscles in the walls of the abdomen. We may, then, get a large number of organs suffering more or less from relaxation or displacement. In the conditions treated of by Dr. McCallum he points out that all cases can obtain a symptomatic cure by a thorough course of Weir Mitchell treatment, in which care is taken that the abdominal wall is thoroughly built up, but this treatment must of necessity be a mere palliative if the conditions originated in uric acid collæmia and its effects on the circulation and muscle power.

The feeding up clears the blood of uric acid temporarily, the massage strengthens the muscles but for a time also, and only the treatment of the uric acid factor can produce a permanent result.

It is clear that such defective circulation will account for the failure to digest and absorb either food or drugs, and also for the putrefactive processes which, under these conditions, take the place of digestion, they in their turn accounting for the changes in the urinary constituents noticed in epilepsy by Drs. Herter and Smith (p. 266); possibly also for the somewhat similar evidence of intestinal putrefaction met with in some conditions of anæmia (see chapter xii.). We shall see in chapter xii. that they probably explain the causation of oxaluria and its frequent association with dyspepsia and hæmoglobinuria.

The fœtid motions met with in dyspepsia, bilious attacks and diarrhœa are, I think, very often due to collæmic putrefaction.

In chapter xii. I give notes of a case in which, with these dis-

turbances of the circulation in stomach and intestines, there was distinct evidence of congestion and enlargement of the liver, associated in some attacks with a temporary albuminuria.

I mention this to show the possible effects of the circulatory disturbances of collæmia on the liver (we can already demonstrate their effects on the kidneys) and to draw attention to the close time relationship between these troubles, a relationship which I hope to show has its foundation in community of causation. This must be my excuse if in the chapters treating of these conditions I am driven to occasional repetition.

My main point in this present chapter can be demonstrated by a simple experiment. Let anyone swallow a few grains of salicylate of soda and watch how long it takes for the reaction with perchloride of iron to appear in his urine. Under normal conditions it may be found in from seven to ten minutes. Let the experiment be repeated when blood pressure is above normal, with headache, bilious attack, or other form of gastric upset, when the pulse is slow and urine scanty. The reaction in the urine does not then appear for a considerable time, possibly, as in the case of epilepsy mentioned before, not for hours (see p. 268). The hourly excretion of urea might here, as in Bright's disease, be used as a test of the good or bad condition of the gastric circulation (see chapter xiii.).

Failure of gastric digestion and absorption is not only a result of collæmia and its circulatory changes; it is a cause of further collæmia, for the failure of digestion and absorption diminishes the blood's income of tissue foods and acid-forming substances, and this, added to the deficient circulation in all the great metabolic tissues, tends towards a feebler metabolism with lessening formation of urea, and of acids and acid salts, and growing alkalinity of the blood and tissue fluids, which thus become better solvents of uric acid, and will take up more as it becomes available.

From collæmia to dyspepsia and from dyspepsia to collæmia, we get a vicious circle which tends to extend and drag the patient down to lower conditions of digestion and metabolism. This must be completely broken through before general improvement is possible.

In the *British Medical Journal*, 1905, vol. i., p. 347, is an article by Dr. H. Batty Shaw and Mr. R. H. Tribe on "Recurrent Vomiting in Children," showing that this is a disease which very often turns later into migraine, and that excess of the alloxur bases—uric acid or xanthin—has been found by several observers in the urine of such cases. Their record leaves me little doubt that the poison is really uric acid, and these cases are but developments of special symptoms in the migraine picture.

I believe that children to the age of 8 or 9, though they have bilious attacks and all the main symptoms of migraine, may be free from headache, because the heart is not strong enough nor blood pressure high enough to produce intracranial pressure and pain. About the age of 8 they may have these, and may then suffer from typical attacks of migraine, while before this they may suffer from recurrent vomiting and other symptoms described by these authors. Similarly we see among adult patients a certain number who suffer from all phenomena of the migraine attack except the headache itself—the biliousness, the vomiting, the failure to digest, the congested liver, are all present, and we shall find probably that blood pressure is high. There are undoubtedly some people whose heads are fortunately, or unfortunately, so constructed that no blood pressure ever likely to occur will cause pain.

In migraine, epilepsy, and collæmia having similar causation, the authors notice the evidence of intestinal putrefactive products, the causation of which in the case of headache and epilepsy I have discussed. In an illustration given one notices the great extent to which wasting has been carried, and another point of great interest is that several of those whom they quote have laid great stress on the value of a large dosage of alkali, especially bicarbonate of soda.

Their record, and especially the extreme debility and wasting met with in these cases, suggest what I have often previously suspected, that many of the marasmic conditions met with in young children (apart from tubercle or other organic disease) may originate in similar toxic conditions produced by uric acid or xanthin. I have noticed that in cases of marasmus the substitution of a natural diet containing vegetables and fruit, and the abstinence from such poisons as meat, meat extracts and meat soups, has been followed by considerable improvement, and even in summer diarrhœa, that most hopeless and fatal of children's diseases, some good may be done in this direction. With regard to marasmic conditions pure and simple, we have in the effects produced by uric acid two important factors which may explain a large part of its phenomena. When we have chronic intestinal catarrh, which is, like all other catarrh, a symptom of rheumatism, we have the very defective digestion and absorption of food, both gastric and intestinal, as the invariable accompaniment of every collæmic attack or uric acid storm. The intestinal catarrh would undoubtedly be greatly relieved by alkaline treatment, and I have long known that bicarbonate of soda was a useful addition to the bismuth mixtures so often used. Indeed, the bicarbonate of soda

is often more useful than the bismuth. Eventually the bicarbonate of soda, by eliminating uric acid, will bring about free capillary circulation, and thus further a more satisfactory state of digestion and absorption from the stomach and intestines. If this is the pathology of these interesting cases we have no difficulty in understanding why so many observers have noted that they eventually develop into migraine in later life, and there is strong reason to believe that a correct uric-acid-free diet taken in earliest years would prevent both sorts of trouble, and that many cases of marasmus or diarrhœa now almost hopeless would be prevented.

Again, in the primary disturbance of gastric digestion putrefaction may supervene, and masses of food in this condition act as irritants in the lower portions of the intestinal tract, exciting more or less local inflammation and diarrhœa.

In these conditions I believe mercury and its salts act, not as local disinfectants within the intestinal mucous membranes, but by absorption into the blood, clearing it of uric acid, with which they form insoluble compounds. Digestion and assimilation are thus allowed to proceed, because the capillary circulation throughout the intestines is restored, and putrefactive formations soon cease.

There may still be patches of gastro-intestinal irritation due to the presence of the products of putrefaction and fermentation; and some diarrhœa may continue from this cause. There will also remain some general lowering of nutrition and debility, and some anæmia, which will require special treatment in addition to keeping the blood clear of uric acid.

But supposing that before the process has been stopped intestinal irritation has become considerable, passing in some places even into slight inflammation, it is clear that when by mercury or other drugs we clear uric acid from the blood we may very probably get a concentration of it in the tissue fluids round about such foci of irritation, and this will be still more liable to occur if, as the result of disturbed digestion, there has been fermentation with excessive formation of acids, rendering the intestinal mucous membranes more acid than usual.

Such a concentration of urates in the fibrous walls of inflamed areas of intestine, as they concentrate round the slightly alkaline fibrous tissues in joints, and in the liver, spleen, and kidney (in several of which they may be present in quantities visible to the naked eye), constitutes what I have named gout of the intestines (*Practitioner*, vol. i., no. 1, 1893), and forms, I believe, the anatomical condition behind such troubles as colic, enteralgia, enteritis and not a few cases of typhlitis or appendicitis.

If there are present such foci of intestinal irritation as the result of dyspepsia, with putrefaction or fermentation of food substances, at a time when a dose of mercury drives uric acid out of the blood, it is little wonder that by further concentrating the urates round the intestinal lesion the mercury should greatly aggravate the trouble and produce severe gout of the intestines.

We have the evidence of Sir A. Garrod and others that urates may thus produce severe inflammation of the intestinal walls, and eventually be deposited there in such quantity as to form visible concretions.

Sir A. Garrod gives notes of the case of a gouty man, aged 50, where, after exposure to cold, gout retroceded to the intestines, producing intense inflammation of the last 18 inches of the ileum, as found after death ("Gout and Rheumatic Gout," Ed. iii., p. 439).

Sir Dyce Duckworth says: "Professor Hayem has recorded a case where enteritis occurred, the villi being strewn with small uratic incrustations"; and further on: "Severe colic, tympanitic distension, enteralgia, and diarrhœa are sometimes distinctly referable to gouty disorder" ("A Treatise on Gout," p. 89).

From these remarks it might be supposed that, though the conditions mentioned occasionally occur as the results of gout, they are rare, and therefore of little clinical importance.

My clinical and experimental experience has, however, convinced me otherwise. I believe a very large number of cases, such as I have mentioned, are neither more nor less than a gout of the walls of the intestinal tube, and that a knowledge of their true pathology places us in a position to effect a satisfactory cure with the drug, giving the best results in cases of arthritis due to uric acid.

I am inclined to regard many cases of slight intestinal colic with marked flatulence as minor conditions of the same thing. These conditions are often produced by cold or acids (uric acid precipitants), and relieved by alkalies or salicylates (uric acid solvents).

Such colic or enteritis can be produced by certain drugs, all of which have the same action on uric acid, viz., that of driving it out of the blood into the tissues. Prominent among these are the metals, mercury, lead, and zinc, all of them forming insoluble compounds with uric acid. I believe that lead colic can be as successfully treated by salicylates as gouty arthritis, and that it is simply an enteralgia or enteritis, produced by the irritant effects of urate of lead in the intestinal walls. The same result can be produced by urate of mercury, urate of zinc, or even urate of soda.

It was my personal experience that first directed my attention to these points, for some years ago (1889 or 1890) I noticed that when I was suffering from gastro-intestinal trouble, such as that which commonly produces an attack of uric acid headache (migraine), and treated this by taking a small dose of calomel, I sometimes produced pretty severe intestinal pain, generally located in or about the right iliac fossa.

On one occasion when a small dose of calomel (gr. i.) acted thus, I thought the purgative action had been insufficient and that a larger dose was indicated; the result, however, was to produce very severe pain which confined me to bed for several days, and even suggested typhlitis.

I then knew little about gout of the intestines, and nothing at all about the solubilities of the urates of mercury; hence, beyond a mental note to avoid, as far as possible, the use of calomel, the lesson was lost.

A year or two later, when taking cocaine for purposes of experiment, I was surprised to find that it was followed on several occasions by a somewhat similar pain; and this, partly due, I think, to cocaine, and partly the result of cold and occasionally wet feet, became chronic with relapses, and awakened my old fear of typhlitis.

I consulted a friend, and, at his suggestion, was deciding to take several months rest and change of climate, when I chanced (still following out my experiments to some extent, or possibly prompted by previous experiences) to take a few doses of salicylate of soda. The effect was magical; the pain was better soon after the first dose, and in two days was gone for good.

I saw that I was not suffering from serious organic disease (though it is serious enough when not treated as gout), but from a gout of the cæcum accompanied by a certain amount of colic, enteralgia aud enteritis, and when I afterwards found out the insolubility of the urates of mercury I understood why this metal had produced the pain on a previous occasion and why salicylate of soda had cured it so completely.

I have had no further anxiety on the score of this intestinal disorder. It has recurred, and I will undertake to produce it at any time with the drugs I shall mention presently. But I can put an end to it in a few hours' time by means of salicylate of soda.

One of the first uses I made of this knowledge was to apply the same argument to lead colic, due to another metal whose urate is insoluble (Garrod). I have shown that, like mercury, it diminishes

the excretion of uric acid and clears it out of the blood, and, like mercury, it produces intestinal irritation and colic. If this is so, salicylate of soda should be useful.

In all cases where I could give it this has appeared to be so, for the symptoms cleared up steadily, the patients doing fully as well as under any other treatment known to me. Colic in which there is no sign of the presence of lead will generally yield to salicylate of soda more quickly than to anything, and I have treated many cases that were clinically typhlitis in the same way, with every reason for satisfaction.

One of these was a relative of my own, a member of the profession. I heard that he was ill with what sounded like typhlitis and that he had taken a dose of calomel shortly before the attack. It struck me that this was a repetition of my own experiences, and I persuaded him to let me add a little salicylate of soda to the mixture he was taking.

The result was as satisfactory as in my own case; he at once began to improve and in two or three days he was up and about, while prior to the administration of this drug it appeared probable that his illness would be a matter of weeks.

The history of this case is as follows: After one or two rather extensive dinners and champagne, he had a little digestive disturbance, and with the intention of putting this right he took a few grains of calomel, and a few hours later was seized with violent pain in the right iliac region. The pain came in attacks which were worse at night and caused nausea. There was ill-defined fulness, with tenderness, and temperature about 100° F. He lay in bed often groaning with pain and with warm poultices constantly applied; a mixture containing nepenthe and carminatives was given and a nurse obtained.

This was the condition of things when, with the concurrence of the neighbour who was looking after him, I added salicylate of soda to the mixture.

There was, I think, no doubt in our minds that we were dealing with typhlitis, or a condition so like it that it deserved the utmost respect, but I felt no doubt from the history of its causation that it would yield to salicylate of soda, and this proved to be so.

Among drugs which have from time to time produced somewhat similar intestinal troubles in myself are, in addition to lead and mercury, zinc (which I have taken as the sulphate and as the phosphide). Dr. Ringer mentions zinc colic ("Therapeutics," Ed. xii., p. 254); and copper, of which he says (p. 252): "Copper

salts taken for a considerable time in small quantities are said to give rise to a condition not unlike that produced by lead, for example, colic with alternating constipation and diarrhœa, and it is even said paralysis of the upper extremities, indistinguishable from that of lead" (see also a note on the effect of peas coloured with copper, in the *Lancet*, 1892, vol. i., p. 1445).

I have had a patient who worked in brass, and had troubles resembling uric acid headache which she attributed to her work. What is described as brass-worker's ague has many points of resemblance to a severe attack of migraine. In these cases headache was no doubt due to an overflow of uric acid into the blood from that which had previously been retained in insoluble combination with copper. We can see that the paralyses originated in neuritis caused by the stasis and thrombosis of the collæmic circulation, just as these processes are seen in the retina in migraine (see p. 212). And we know that urate of copper is insoluble, for a process for estimating uric acid is founded on the fact (Arthaud and Butte, *British Medical Journal*, 1890, vol. i., p. 495). The parallel, therefore, with lead and mercury is complete.

In the Epitome of the *British Medical Journal*, 1902, vol. i., p. 33, there is the record of a patient who, having had his appendix removed, yet suffered again (obviously not now in the appendix but in the neighbouring fibrous tissues), and was found to be the subject of lead colic; also a still more interesting case in which an attack "began as a typical lead colic and ended fatally some days later with perforated appendix"; and the record proceeds: "The question is asked if by any chance plumbism might not of itself be the cause of appendicitis."

My reply would be: "Certainly, and not lead only but any of the other metals mentioned, also cold, acids, food residues, local irritation and inflammation, however caused, anything, in fact, that will precipitate uric acid into the fibrous tissues."

I have mentioned the pain produced by cocaine; cocaine also diminishes the excretion of uric acid, and acids, nux vomica and sulphates, especially sulphate of soda, occasionally act in the same way and cause similar intestinal pain. Exposure to cold, or cold feet in winter, occasionally produces the same result, and all these factors have the same action on uric acid; they diminish its excretion in the urine, clear it out of the blood and drive it into the liver, spleen and fibrous tissues, especially into any fibrous tissues where the alkalinity is diminished by previous irritation or inflammation. They produce this effect on uric acid either by forming insoluble

compounds with it, as in the case of the metals, or they diminish the solvent powers of the blood by lessening its alkalinity, and under slightly different conditions any of them may produce gout of a joint instead of gout of the intestines.

No one, I suppose, will deny that there is a large amount of fibrous tissue in the walls of the intestines, and if the fibrous tissues in fascia, tendons, and joints, and those in the respiratory and upper digestive passages are liable to the deposit of urates when alkalinity is diminished by cold, injury or irritation, I see no reason why the fibrous walls of the intestines should not be affected in the same way.

The case quoted from Sir A. Garrod's book might have a causation somewhat as follows:—

A gouty man has more or less acute intestinal irritation (of dyspeptic origin) causing some nausea; this produces collæmia; on this follows exposure to cold, which raises acidity and drives the urate out of the blood again, and, as in other cases, a large amount of it goes into that piece of fibrous tissue which is most irritated and least alkaline—in this case the fibrous structure in the walls of the last eighteen inches of the ileum; by this extra urate the irritation is still further increased, acute gouty inflammation of this portion of intestine ensues, and becomes so serious as to cause death.

I have no doubt that if an extract had been made of this portion of the ileum it would have contained far more urate than an equal weight of any other portion of the intestines. We see from the points mentioned by Sir Dyce Duckworth (previous quotation) that the gout may proceed until the deposit of urate is visible.

I had an opportunity of testing a piece of inflamed intestine for uric acid in the case of Alice C., aged 12, admitted under my care at the Royal Hospital for Children and Women on November 11, 1895.

She had been suffering from appendicitis or perityphlitis for some three weeks, and this had probably gone on to suppuration before she was seen.

As her condition was unfavourable for operation, she was put on salicylate of soda, given by rectum; but this did not produce any marked effect, and she died with general peritonitis. Probably the salicylate failed because suppuration had already taken place. In my experience it is useless in gouty arthritis when this is the case.

At the *post-mortem* a local abscess round the appendix was

found, which had burst into the general peritoneal cavity shortly before death.

I took a portion of the cæcum with the appendix at the seat of the local abscess, and also a portion of the colon from the opposite side of the abdomen near the splenic flexure, and tested them for uric acid in the ordinary way.

I found in the portion of cæcum and appendix ·053 gr. of uric acid per ounce, but in the splenic flexure so little that I could not feel certain that there was any; while in the extract of cæcum the precipitate with nitrate of silver was quite visible.

It is probable that the pus of the local abscess would have contained more uric acid had we secured it, and that the inflamed intestine would have contained more earlier in the disease.

I lay no weight on my results in this single case, but record it with the object of getting others to repeat my observation whenever they have a chance, either in perityphlitis or the colic produced by lead or other metals.

We have some evidence pointing in the same direction in the part of the intestine commonly affected; why should the last eighteen inches of the ileum or, in my experience, the cæcum and lower ileum, be the parts affected?

I suggest that the reaction of the intestinal contents has something to do with it; it is well known that those of the large intestine have an acid reaction, and it is not improbable that alkalinity is diminished in the small intestines before the ileo-cæcal valves are reached.

M. Bouchard ("Leçons sur les Auto-intoxications," p. 172) has shown that in certain dyspeptic conditions, especially in dilatation of the stomach, there is an excess of acid throughout the whole intestinal canal, and such acidity may cause local irritation and thus form the starting point for a concentration of urates in the intestinal walls and an attack of gout.

Any local irritation due to impacted fæces or foreign bodies may act thus, setting up a local inflammation with fall of alkalinity, which is soon complicated by a concentration of urates on the irritated spot. In this way irritation in the vermiform appendix may precipitate a local attack of gout, which, as in other parts—the joints and valves of the heart, for instance—recurs until a more or less extensive lesion (typhlitis and eventually perityphlitis) is produced.

Recent writers on this subject generally make use of the term appendicitis, and if the trouble originates in the appendix there is no objection to this. As regards its gouty or rheumatic origin

it makes no difference whether it begins in the appendix, the cæcum, or the lower ileum, as in the case recorded by Sir A. Garrod. The only thing that concerns us is that these portions of intestine contain fibrous tissues upon which urates may be precipitated if their alkalinity is diminished by such things as dyspepsia, cold or irritating substances. And the irritation so caused may recur and lead to ulceration and sloughing, just as in any other fibrous tissues.

It is interesting to note in this connection that Dr. G. S. Keith, writing to the *Lancet* on October 29, 1904, says with reference to the apparent increase in cases of appendicitis, that this disease was extremely rare among his patients during a long period of practice in Edinburgh, and that he has heard of no case for the last twenty-five years among his old patients. In this connection we should bear in mind that the Scotch eat much less meat and suffer less from gout than the English. And Dr. Keith goes on to say: "I have always objected very strongly to very strong feeding, and to the use of butcher's meat, which was introduced some sixty years ago, and generally adopted by both the profession and the public. This mode of living has been followed now by three generations, and, as I have shown elsewhere, to the great deterioration of the health and strength both of rich and poor."

Statistics which I have elsewhere mentioned show that there has been a great increase in the consumption of meat per head of the population in this country in the last thirty years, and Dr. Keith suggests that there was a similar increase in Scotland some sixty years ago.

I may mention also a very interesting paper by Prof. Auguste Broca, M.D., which was published in the *Lancet*, 1906, vol. i., p. 1583, and in this he says: "From the observations made at every age and in every country, it appears that the general opinion of medical men is to the effect that an excess of flesh diet may be the origin of enteritis predisposing to appendicitis."

Then Dr. Chalmers Watson, to whose statistics on the importation of meat I have already referred, says in a letter to the *British Medical Journal*, 1906, vol. i., p. 947, in reference to his experiments on animals, "I have found that the administration of an excessive meat diet is frequently followed by structural changes in the intestinal tract, which are invariably most pronounced in the region of the cæcum."

This experimental investigation gives a most interesting corroboration of my own clinical experience. I have over and over again

found, both in myself and others, that as the excessive meat diet was given up the conditions have steadily improved, especially in the region of the cæcum and appendix, so that those who on wrong diet were rarely or never free from trouble in this region, and were often quite unable to eat such things as simple fruit or tender nuts, these same people after several years on correct diet, and removal by this correct diet of their stores of uric acid and general rheumatic troubles, have shown the most marked improvement in the intestine of this region, and were eventually able to take the above-mentioned foods not only occasionally, but as part of their regular daily diet.

But, it will be said, if the reaction of the intestinal contents has anything to do with the gout attack and its localisation, then surely the stomach should be the place of all others in which these gout attacks should occur.

We all know how the stomach is prevented from digesting itself by the free circulation of alkaline blood in its walls, but let there be local irritation, inflammation or stasis, then the acidity of the contents does affect the structure of its wall, and it proceeds to digest itself to a certain extent. I can quite believe that such a local irritation may be sustained and repeated by urate irritation. Sir Dyce Duckworth mentions the conditions found in one or two cases of gout of the stomach (previous reference, p. 89). And I have seen a number of cases of what I suppose would be called gastralgia where the pain has yielded in the most decided manner to salicylate of soda. In one such case the trouble had continued for more than twenty-five years ; it came in attacks lasting seven to ten days, worse in winter or on exposure to cold and better in warm rooms. The attacks were increased by calomel, aperient waters, or acids, and there was a family history of gout; the pain was in the epigastrium, and was described as being like toothache in the stomach. It is not a little remarkable in how many cases of gastric dyspepsia one finds salicylates useful in relieving pain.

I suggest that those who are able to estimate the amount of lead in the organs and tissues of fatal cases of plumbism should estimate the uric acid to see whether they are present in their combining proportions, and therefore probably as urate of lead.

Professor Oliver, in his interesting work on "Lead Poisoning" (p. 38), points out that during an attack of lead colic the pulse becomes hard, resistant and slow, and the urine scanty and of high specific gravity ; the action of urate of lead will explain every fact here mentioned.

While the lead is causing retention of uric acid (its first action)

the pulse is quick and soft, the capillaries are free, and the urinary water profuse; but later urate of lead, which carries uric acid out of the blood and so frees the capillaries, is deposited in various organs and tissues, among others in the walls of the intestines. Here it gives rise to pain and colic, and this changes the whole condition, producing the rebound or second action of lead.

The intestinal pain and colic produce nausea and failure of digestion and absorption. As a result the acidity of the urine falls and the alkalinity of the blood rises. This dissolves some of the urate stores and floods the blood with uric acid, which in turn causes the obstructed capillaries, slow high tension pulse, and scanty urine.

An interesting case in which appendicitis occurred in association with plumbism is recorded in the *Lancet*, 1899, vol. ii., p. 171, and I wrote a letter which appeared on p. 238, pointing out that there was no difficulty in explaining this association if appendicitis be a gout of the fibrous walls of the intestine. The effect of lead in producing gout is well known, and in this case (in which there was no doubt about the presence of lead) it might quite as easily produce a gout of the intestine as a gout of the hand or foot. The case was parallel with those above mentioned, the metal being mercury in one case and lead in the other, and I have little doubt that the salicylates would settle the questions of diagnosis and treatment.

The same series of events can be ensured by any drug or combination of drugs with the same effect as lead on the solubility of uric acid, and what I have called the rebound after mercury, opium, zinc, cocaine, or acids with nux vomica, reproduces all the phenomena attending lead colic as described by Professor Oliver.

But it will be said if the rising alkalinity dissolves the urate of lead it should remove that which is irritating the walls of the intestine and put an end to the colic. So it eventually does, and this is Nature's mode of cure; but inasmuch as there is a considerable amount of local irritation and inflammation in the intestinal walls the alkalinity of the fibrous tissues is lower here than anywhere else. This is the last place the rising alkalinity affects, and meanwhile the pain and inflammation go on.

But if at this time salicylate of soda is given it acts (as I have shown) best in conditions of low alkalinity, and it dissolves and removes first the urates in the irritated intestine, because that is the place where alkalinity is lowest. Hence, as observed, it very quickly relieves the colic and does this equally well whether dealing with urate of lead, urate of mercury, or urate of soda, and for the

same reason it is useful in gout and rheumatism (*Med.-Chir. Trans.*, vol. lxxi.).

But urates may undoubtedly affect other structures containing fibrous tissues, and, as mentioned in the previous chapter, I have seen them so affecting the pharynx, larynx, trachea and large bronchi or the œsophagus. Such inflammations are often brought on by exposure to cold in the same way as other gouty inflammations of fibrous tissues. When gout affects the œsophagus it causes severe pain at one spot behind the sternum, and every mouthful of food swallowed seems to pass at one point over an extremely tender bruised surface. Fortunately a single dose of salicylate almost completely removes it, but I believe that when not so treated it may sometimes spread to neighbouring fibrous tissues, as the pericardium or the diaphragm, and produce more serious results.

Further, there is this point of interest with regard to such uratic inflammations of fibrous tissues, that, while they are commonly produced by the local effects of cold, when there are salicylates in the circulation cold has no power of producing them. Warmth or the administration of alkalies will now make them worse, and cold or administration of acids better (see Treatment of Pneumonia and Catarrh in the previous chapter, the record of my own experience with reference to fig. 74, and the record of similar facts in others in chapter xvi.). So far as I know there is no explanation of these facts except the well-known differences in the solubility of uric and salicyl-uric acids respectively.

For a case where colic and enteritis followed sudden exposure to great cold, see *British Medical Journal*, 1898, vol. ii., p. 895.

Uric acid is soluble in alkalies and insoluble in acids; hence it is precipitated by cold, which diminishes locally the alkalinity of the blood and tissue fluids.

Salicyl-uric acid, on the other hand, is soluble in slightly acid fluids, insoluble in alkaline ones; cold therefore aids its solution and warmth hinders it. As recorded by many observers, warm clothing or warm weather makes gout or rheumatism worse under salicylates, while keeping the affected parts cool makes them better, and it would be interesting to know how often salicylates have been blamed for not curing gout or rheumatism through ignorance of this fact and consequent neglect to keep the parts cool. As I shall point out in chapter xvi. salicylates act very badly in the warm climate of India, and some practitioners have refused to consider that the arthritis met with in India is rheumatism because salicylates thus

fail to relieve it. If they could keep their patients cool this difficulty about names would disappear, and salicylates would cure uric acid arthritis in India as they do here; but even here they cure best those in which the urine is most acid, *i.e.*, the acute cases.

For the same reason salicylates do not act well, as noted by Dr. Buckler, when the urine is neutral or alkaline, but he did not know the reason of this, or that he could make them act well by giving acids in alternate doses or keeping his patients cool.

These inflammations can be cured by either alkalies or salicylates separately, but they are made worse by a combination of the two, and for those who still regard rheumatism as a disease of microbic origin, this fact remains, I believe, inexplicable. (See "Salicylates in Diagnosis and Treatment," *Medical Record*, New York, December, 1907.)

I have long thought it possible that considering the way in which carcinoma tends to attack seats of local irritation, it may often have its way prepared by the chronic and recurrent irritation produced by urates in the tissues. This has been further suggested by the interesting articles published by Mr. D'Arcy Power and others (*British Medical Journal*, 1893, vol. ii., p. 830; and the same journal, 1895, vol. i., p. 910; also *Lancet*, 1893, vol. i., p. 1443).

Cancer is said to be rare among vegetarians (*British Medical Journal*, 1888, vol. ii., p. 29; and *Lancet*, 1888, vol. ii., p. 552), and Dr. Berkhart has pointed out the resemblance between the structure of a gouty tophus and a sarcoma (*Lancet*, 1893, vol. ii., p. 1500).

A case recorded by Sir W. Gowers in the *British Medical Journal* (1894, vol. ii., p. 1222), of a patient who suffered from gastric troubles, was treated by oxide of silver, with the result that he got argyria with wrist-drop, became very gouty, and eventually died of cancer, seems of interest. Sir W. Gowers believed there was no connection between his other troubles and the new growth; but if there is anything in the above suggestions, surely this man's tissues were subjected to very widespread irritation by urate of silver. Mr. Roger Williams, *Lancet*, 1898, vol. ii., p. 481, while drawing attention to the "highest on record" death-rate from cancer in the Registrar-General's report, mentions the pregnant fact that "the consumption of meat has for many years been increasing by leaps and bounds, till it has now reached the amazing total of 131 lb. per head per year, which is more than double what it was half a century ago, when the conditions of life were more compatible with high feeding." We not only eat more

meat but are in a far worse condition for eliminating uric acid, and the *Lancet* (1902, vol. i., p. 1121) acknowledges that cancer has increased in the last thirty years. I have no space for statistics and their analysis, but I note that a recent report by the Medical Officer of the Scottish Widows' Fund shows a decided increase in deaths from such diseases of uric acid origin as Bright's disease and cerebral hæmorrhage, which with bronchitis and heart failure constitute the final endings of about four-fifths of the diseases treated of in this volume. It is interesting to note the increased death-rate from these diseases running parallel with the increase of that from cancer and with the increased consumption of meat.

Several of these points have been noticed in an article by Sir W. M. Banks (*Lancet*, 1900, vol. i., p. 684), in which he attributes the increased cancer death-rate largely to "richer and more abundant food," of which males eat more than females, and consequently suffer more from cancer.

He points out that in London and the Thames Valley the best living prevails, with the highest cancer death-rate, and among his list of specially affected occupations are many obviously exposed to an excessive intake of uric acid and its retention, as commercial travellers, butchers and plumbers, lead acting like silver in the above-mentioned case.

I observe that the *Daily Telegraph* (November, 1901), in commenting on the Report of the Registrar-General for Ireland for the year 1900, in which the cancer death-rate for Kerry (where a butter-milk, Indian meal and potato diet is prevalent) is only 2·76 per 10,000, while that of Armagh (with a mixed and animal diet) is over 10 per 10,000, remarks: "It would be a curious thing were it established that the humble potato is a counteractive to cancer."

This whole record is interesting, for not only is the diet of Kerry almost exactly the one I should choose to prevent cancer, —though it would even better accomplish its purpose if bacon and tea were left out—but the potato to which the *Daily Telegraph* attaches importance has an action exactly the reverse of that of lead and silver. These latter retain uric acid, and doubtless lead to its widespread deposition in the tissues; the potato means a daily dose of alkali, which leads to the solution and taking up of uric acid from the tissues, and its excretion. It will be seen in chapter xvii. that I make considerable use of potatoes for this purpose in prescribing diets for arthritis. For a most interesting record of cases where natives of vegetable-feeding nations got cancer apparently without any possibility of infection when they began to eat meat

like Europeans, and only those who ate meat got it, see an address by Sir W. MacGregor, *British Medical Journal*, 1900, vol. ii., p. 982.

Dr. Braithwaite suggests that excess of salt in diet is a probable factor in the causation of cancer (*Lancet*, 1901, vol. ii., p. 1578), and this interests me because salt (sodium chloride) is, like other salts of mineral acids, a precipitant of uric acid and hinders its excretion, thus having similar action to that of the metals and opposite action to that of potatoes. He says in the *Lancet*, 1902, vol. i., p. 400: "My point is that whenever cancer exists two at least of four factors must be present: one of these is salt in some excess, the other is a local irritant."

There cannot, I think, be a doubt that uric acid is just such an irritant, and salt makes it more so by retaining it in the body, while potato makes it less by eliminating it through the kidneys.

It is my experience that sodium chloride increases arthritis in the rheumatic by retaining uric acid, and headache in the migrainous by causing fluctuations in excretion.

Dr. Braithwaite would attribute the cancer among natives of India to their eating salt, but I attribute it to their pulse diet, the uric acid in which is retained and accumulated by salt.

Sir W. M. Banks points out an observation of Mr. Moore, of the Middlesex Hospital (see *British Medical Journal*, 1902, vol. i., p. 718), that "cancer is eminently a disease of persons whose previous life has been healthy, and whose nutritive vigour gives them otherwise a prospect of long life." It is precisely the vigorous who tend to retain uric acid, and who therefore have much of this local irritant in their tissues; the weakly and dyspeptic excrete it almost as fast as they can form and swallow it—they therefore have less in their tissues, and are less liable to cancer.

Egypt appears to be another place in which a low cancer death-rate accompanies a low consumption of uric-acid-containing foods; for the facts, see Mr. Roger Williams in the *British Medical Journal*, 1902, vol. ii., p. 917, and compare this with my observations on diet and disease in Cairo in chapter xvii.

In the *Medical Press and Circular*, June, 1904, I pointed out the possible relation between uric acid and cancer and the probable effect of solvents and precipitants in hindering or hastening its onset. I also drew attention to the very wide expanse of the field of modern life in which one is liable to come into contact with retentive substances. But a few instances must here suffice, such as lead and lime in drinking and cooking water, lead, mercury, copper, zinc and tin in many preserved foods; and several of these

metals are used in contact more or less directly with preserved foods, as in tinned foods, and in the cooking and preserving of foods, and lastly, the use of many of these metals in medicine, as of zinc, copper, silver and gold in nerve diseases, of lead as a styptic, and of iron as a treatment for anæmia. In those people who are full of uric acid in every tissue there is almost no end to the local precipitation that these substances may produce, and as I said before, each small local deposit acts as a uric acid filter until all has been completely redissolved and removed, and in certain not uncommon conditions, *e.g.*, those of high feeding and high acidity, years may elapse before this removal is complete.

Some points of great interest are also mentioned by Dr. R. Kirk, *British Medical Journal*, 1903, vol. ii., p. 1528, where, in a short article on paraffin cancer, he shows that contact of the skin with naphtha mixture causes, first of all, intractable eczema; second, small pimples, which tend to become boils and then ulcers; and third, that of the ulcers so formed "a considerable proportion took on malignant characters." He concludes his paper as follows: "These tumours were all epitheliomata, and the conclusion one must come to is that long-continued irritation certainly does predispose to the production of malignant disease."

Here, then, we have one more instance of chronic irritation assisting in the production of cancer, and after what has been said above about the causation of eczema by uric acid is it to be doubted that a gouty man, or one whose blood is most heavily charged with uric acid, would suffer most from the paraffin, and that the local lesion once produced would be in him also least ready to heal, for uric acid not only produces local irritation, but adds itself on to and so increases and prolongs any local irritation otherwise produced? It also interferes with the nutrition of the skin, and so hinders the healing of wounds of all kinds. The mention of boils also is interesting, for these are often contagious, and are probably due to the inoculation of the irritated skin, and it is at least possible that the cancer which develops later on is also due to an inoculation of the ulcers, which remain open and exposed to all kinds of dirt for so long a time. Then I have pointed out that there is at least one contagious disease, namely, a common cold, which effects an easy lodgment in the mucous membranes of those whose circulation is loaded with uric acid, but which often does quite fail to affect those who are relatively free from this substance. Further, if acute rheumatism were to prove to be in any way connected with a microbe it would be a parallel

instance of the same thing, that is, the microbe could not affect those who were free from uric acid, and we already know that acute rheumatism, or, as I prefer to call it, "acute uratic arthritis," can be produced or precipitated by several different kinds of microbes, *e.g.*, those of scarlet or enteric fever or of influenza, and when cases of infectious acute rheumatism are described it probably means that one of these microbes has passed from person to person and produced prominent arthritic symptoms in each. In each case it affected the excess of uric acid in their body, and my point is that those whose blood and tissues are free from excess of uric acid are not so affected by microbes. If this is so we can at once see how an excess of uric acid in the body may, by favouring chronic local irritation and ulceration, pave the way for the incidence of cancer. I do not wish to assert that cancer is due to a parasite, and the facts mentioned above as being recorded by Sir W. Macgregor are against this causation, to some extent, but I do desire to suggest that the facts which I have mentioned above in mere outline should not be entirely neglected in any investigations that have for their object the clearing up of the causation of cancer.

In the pamphlet I drew the following conclusions: (1) Cancer tends to affect seats of local irritation or ulceration. (2) Uric acid is responsible for more widespread and chronic local irritation in all the tissues of the body than any other known substance. (3) Insurance statistics seem to show that cancer is increasing side by side with many other diseases which are no doubt due to uric acid, as more and more uric acid is poured into the body in flesh, soup, meat extracts, tea and coffee, all of which are consumed much more largely at the present day than they were thirty years ago. (4) Countries where the diet is, to a considerable extent, uric-acid-free, suffer but little from cancer, while there is some evidence tending to show that when uric acid is present in excess, first in the diet, and as a result in the blood, the incidence of cancer is increased by substances which tend to precipitate uric acid in the tissues and is diminished by substances which aid its solution and removal from the body. (5) Lastly, I point out that if further statistics support those I have mentioned above in showing that there is a definite relation between cancer incidence and the amount of uric acid in the body, we can at once attempt prevention by cutting off supplies of uric acid and giving solvents, just as is already being done with success in many other conditions which are more clearly and obviously due to uric acid.

Later I added the following suggestions as to treatment:—

(1) The use of a strictly uric-acid-free diet.

(2) A decided diminution in the quantity of food, as cancer coincides with high nutrition. Low nutrition is not only a solvent of uric acid, but tends to diminish pain, probably by lowering blood pressure.

(3) The use of heat, as a hot air bath, every day. This is also a solvent of uric acid, and relieves pain, probably in the same way as (2).

(4) The administration of direct solvents of uric acid, *e.g.*, alkalies or salicylates, with the same object. Thus salicylates and opium may sometimes be administered together for the relief of pain with considerable advantage. Opium alone, though it relieves pain, may do harm, as it retains uric acid, but salicylate given with it will prevent its retentive effect while not interfering with the relief of pain.

I have seen some cases which appeared to do well on solvents, and I notice a record of improvement in a case treated by salicylate of uranium in the *Lancet* (1905, vol. i., p. 387).

Mr. Roger Williams returns to the subject (*Lancet*, 1904, vol. ii., p. 445), and gives numerous figures from which he concludes: "Taking all these facts into consideration there can, then, be no doubt as to the reality of the increase in the cancer mortality."

He also devotes considerable attention to the causes of the disproportionate increase among men; but from the standpoint of causation by uric acid it suffices to remark that men always suffer more than women from gout and retention for well-known reasons.

With reference to the causation of cancer of the intestinal tract it is interesting to remember how much irritation in various parts of the intestines is produced by uric acid, though this causation is often overlooked and is called gastralgia, enteralgia or colic, without thought as to what underlies these names.

It is not, I think, without significance that the great majority of cases of male cancer are found in the alimentary tract. I link this with the fact that men being stronger and having more hearty appetites are more liable to suffer from excess of food, excess of uric acid, and therefore irritation in the digestive organs, while the excess on the female side is chiefly met with in the uterus, the organ which during sexual life is most liable to irritation month by month in the changes of circulation and nutrition. These facts admit of a simple explanation when we remember that uric acid is apt to be precipitated on seats of irritation and to increase that irritation, and that cancer is likely to originate in such foci of chronic irrita-

tion. There is, I think, no room to doubt that many of the chronic irritations, resulting in more or less increase of fibrous tissue, to be met with in the uterus are mere results of rheumatism, that is of uric acid irritation.

But to return, my experience with gout of the stomach and intestines has been shared by others. I notice in Dr. Goodhart's work on "Diseases of Children," Ed. ii., p. 545, a frequent stomach-ache is described as a "feature of the rheumatic child," and he mentions that Dr. Marshall uses salicylate of lithia for this complaint, "he thinks with great advantage."

I have myself seen several cases in which persons who had indulged in excess of acid drinks in the summer, got more or less severe stomach-ache; possibly some of these cases also are really gouty enteralgias, the acid acting in the same way as the drugs mentioned.

Dr. G. A. Sutherland, writing "On some Symptoms associated with the Uric Acid Diathesis in Children" (*British Medical Journal*, 1892, vol. i., p. 856), mentions two cases of inflammation of the vermiform appendix, with marked tendency to recur, and suggests that the calculi found in the vermiform appendix are composed of uric or oxalic acid.

I am indebted for the notes of the following case to Dr. G. D. Logan, of Ecclefechan, the treatment which he adopted with success having been suggested by my writings on this subject.

"Called at 2 a.m., on March 15, 1893, to a case in the country, and asked to bring morphine with me. Found a woman, unmarried, about 24 years of age, suffering from severe abdominal pain and retching. Had arrived the previous day from Glasgow, where she had been for some weeks previously more or less confined to bed with similar symptoms.

"Illness began in January, 1892, with a severe attack of diarrhœa, which gradually turned into dysentery, and though under constant treatment, she had never quite recovered from the looseness of the bowels and pain. In October of the same year she broke down completely, was sent to bed, and had a course of blisters and iodine on the abdomen, with morphine injections. As this gave no improvement she saw a consultant, who said that her womb and appendages were normal, that she was suffering from some neurosis, and advised a course of massage. This she had for a month; says she felt worse for it, and latterly could not bear the pain of rubbing.

"For the last three weeks the pain had been getting more

severe, and she had vomited almost everything taken. She now requires two injections of morphia daily (gr. ½ each), and can get no rest or sleep without them. She had for years been subject to severe, often 'recurring nervous headaches.' She had on one occasion been confined to bed for six months, as the result of a fall injuring her spine, but without any obvious lesions. She is not hysterical.

"On examination I could find nothing abnormal but the tenderness on pressure all over the lower part of the abdomen; her hands were very shaky, and she was much run down in strength.

"I thought it would be a good test case for the treatment you advise, especially with the morphine habit she had developed. I stopped the morphine at once. I ordered fomentations with belladonna for the abdomen. Soup and milk for diet, and a mixture with soda salicylate, nux vomica and gentian.

"After the second night she was able to get sleep, though she missed the morphine greatly, but at the end of a week she did not miss it at all. She got six or seven hours refreshing sleep every night, and the pain was much less.

"In ten days she was out of bed, and in three weeks she was able to go out walking. Had an excellent appetite, pain all gone, bowels quite regular, sleeping perfectly, and since then she has remained quite well."

This is an extremely interesting case, for it illustrates so completely many of my points.

First the "nervous headaches," which, I have little doubt, were due to uric acid, then the diarrhœa which became chronic, doubtless with considerable local irritation in the intestines. On the patches of local irritation urates were from time to time concentrated, and the treatment by morphine, which for a time cleared the blood of urates, would favour their action in keeping up the intestinal irritation. As soon as a drug was given which removed uric acid from the body in place of causing its storage in the tissues, the whole thing cleared up; the trouble was due to precipitants and relieved by solvents.

I must congratulate Dr. Logan on the thoughtful care which led him to apply my reasoning to this case, and on the great success he obtained when others had failed.

I have seen and heard of quite a number of more or less similar intestinal or abdominal pains speedily relieved by the administration of salicylates, or of similar troubles with chronic diarrhœa relieved by the uric-acid-free diet.

Thus Dr. Charles E. Lockwood, of New York, writing in 1894, mentions a lady who suffered from pain and soreness in the neighbourhood of the cæcum, and had one of her finger-joints enlarged; he reported that the pain and soreness began to leave her after the first dose of salicylate.

Dr. John Watson, of Newbury, Berks, reports the case of an old gentleman suffering from very severe gouty gastritis; potash and soda with bismuth were given for a week or two with little success, when, coming on my article in the *Practitioner* (previous reference), he was induced to try salicylate of soda; "the effect was simply magical, he lost all pain after taking the first dose, and has had none since; his dyspeptic symptoms have almost entirely vanished after four days' treatment, and the drug has acted like a charm."

Dr. B. Yeo wrote about rheumatic perityphlitis in the *British Medical Journal*, 1894, vol. i., p. 1189, and I recalled my previous writings in a letter to the same journal, p. 1413. Interesting cases of appendicitis cured by salicylates are recorded by Dr. Brazil in the *British Medical Journal*, 1895, vol. i., p. 1142, and Mr. J. E. Fraser, p. 1320, points out that morphine may do harm, a fact also noticed by Dr. Yeo, and which is in evidence in Dr. Logan's interesting case. I see also in the *Lancet*, 1896, vol. i., p. 640, the record of a case of rheumatism of the orbital cellular tissues, followed later by perityphlitis, both troubles yielding to the administration of salicylates.

Further experience has convinced me that these are no isolated instances, and that multitudes of abdominal and pelvic troubles, all affecting fibrous tissues, and called peritonitis, enteritis, gastritis, even perhaps gastric ulcer, metritis, perimetritis, cellulitis, ovaritis, &c., are, like typhlitis, perityphlitis and appendicitis, nothing but uric acid irritation of fibrous tissues, and that if this was diagnosed and properly treated many years of suffering and numerous operations would be rendered unnecessary, while if a uric-acid-free diet were general such troubles would only occur in the few cases where they are the direct result of mechanical causes.

Did space permit I could give notes of case after case where patients have had their abdomens explored, their stomachs incised, and various pelvic organs more or less mutilated or removed, and yet the pains continued. These pains yielded at once and permanently, however, to well-directed treatment of the uric acid factor.

To such sufferers I suggest that when 60 to 90 grs. of bicarbonate of soda in the twenty-four hours gives decided relief from pain, it is worth while to try the more permanent effects of a uric-acid-free diet before operation is chosen.

It must be remembered, however, that when the trouble has gone on to suppuration there is nothing for it but operation, for neither alkalies nor anything else will relieve.

One patient inquired, "If it is rheumatism, how did I get contraction of the opening of the stomach (pylorus)?" I answered, "In the same way as you got thickening and contraction in your right knee from rheumatism there."

A similar pathology explains chronic throat troubles, such as pharyngitis, laryngitis, post-nasal catarrh with more or less enlargement of the cervical glands, which the above-mentioned patient also had.

I notice with regard to typhlitis, colitis, and appendicitis, Sir F. Treves says (*Lancet*, June, 1902) that undigested residues of food are an important cause; but it is, I think, obvious that they are only partly so, for salicylate or alkali may cure, as we see in this chapter, and yet neither can remove an undigested residue.

Again, why do these inflammations so often come on at night? Why, after exposure to cold, as with cold and wet feet, why are they made worse by acids? Why is colic brought on, perhaps in the most violent way, by acid fruit or an acid drink, when there are perhaps no undigested food residues at all?

The answer is, I think, that undigested food residues are but one part of the causation, and they act by bringing about the local precipitation of the real cause, namely, uric acid.

All these troubles are really gout of the fibrous tissues of the intestines, which, when it is slight, causes merely irregular muscular contractions (colic), when more severe, inflammation of the fibrous walls of the intestines spreading eventually to the peritoneum; just as with the heart we get endo-, myo- and pericarditis as the result of similar urate irritation (rheumatism) (see chapter xvi.).

This pathology enables us to explain all the facts instead of merely a part; alkalies or salicylates cure by removing the urate just as in rheumatism of the heart; they do not remove the undigested food residues, but these are of little consequence when there is no urate to be precipitated by them and when this urate can no longer act as a uric acid filter. Such undigested food residues merely cause a little local irritation, but in a gouty subject all local irritation entails a precipitation of urate and so lights up a progressive irritation, going on to inflammation.

A subject who is pretty free from uric acid may have the same

local irritation from undigested food residues without any disease following. Again, two men may drink the same wine or cider or eat the same acid fruit; one gets colic, the other does not; that one gets colic who had most uric acid in his blood at the time he took the acid. Hence the danger of taking these things when hot and fatigued, for heat and fatigue bring excess of uric acid into the blood.

A man who has once had colic or appendicitis is always more liable than one who has not had it, just as a man who has once had gout in his big toe is liable afterwards to have an attack from slighter and slighter causes (see uric acid filter experiments, p. 177). Here is the danger of exposing the abdomen to cold winds or taking cold drinks when hot and fatigued, for the uric acid which is plentiful in the blood is precipitated locally by the cold, causing colic or inflammation.

This also explains why a man who has suffered from these things is nevertheless quite immune either to cold or acids when he is taking a course of salicylates, or has enough alkali in his blood to make his urine alkaline.

If he is only taking a little alkali he is more liable to suffer from acids and cold than ever, for there is plus uric acid in his blood and these can precipitate it; but if he has enough to make his urine alkaline, the alkali overcomes the cold and the acid and no harm results.

The pathology of colic is the same; any acid fruit may cause flatulence and colic in a person with some plus uric acid in his blood, but not if he has plenty of alkali or salicylate to hold it in solution.

Uric acid pathology explains all these facts, mere local irritation from food residues cannot.

If in any case a uric acid solvent relieves, but the trouble tends to recur each time the solvent is left off, there is probably some undigested residue which should be swept out by a dose of ol. ricini.

In the *British Medical Journal*, 1902, vol. ii., p. 1759, there is an interesting paper by Dr. T. Stacey Wilson on "Colon Catarrh," in which I was specially interested because in speaking of treatment he says, "The key to the treatment of this disease is, in my opinion, the recognition of its relation to gout and the uric acid diathesis, and also the recognition of the fact that it is a catarrh of the colon."

And in the earlier part of the same paper he refers to the value

of salicylates in treatment and to my theory and experience as explaining their action.

I quite agree with all that Dr. Wilson says on this matter with the single exception of his reference to that product of the ignorant imagination (the uric acid diathesis). As a matter of fact, catarrh of the colon, as of the nose, throat, or any other organ of the body, is simply rheumatism, and, like all other rheumatism, is due in nine cases out of ten to wilful and quite unnecessary swallowing of the uric acid produced by other organisms; if man had to deal with no uric acid save that which he himself produces in his own organism, he would, I believe, rarely suffer from any of these troubles.

I note also in the *Lancet*, 1904, vol. i., p. 502, an interesting article by Dr. Alex. Forsyth on "Cæcal Concretions," in which he says that it is possible by means of injections to wash out such concretions, together with a considerable quantity of gelatinous mucus, which has apparently been forming a more or less complete covering over them. Here, again, I believe that we have a condition of catarrh, and that such concretions and such throwing out of gelatinous mucus around them are specially to be met with in rheumatic subjects who suffer from gout of the intestines in one form or another, and I have gathered from my experience that the causation of these concretions is somewhat as follows: The patient who suffers from gout or rheumatism swallows, let us say, some deficiently cooked and, perhaps, deficiently masticated particles of nut; these pass down the bowel (and it is no uncommon experience to see such particles pass practically undigested with the motion) as far, let us say, as the cæcum, and there they lodge in a mass of mucus, the product of previous rheumatic or catarrhal conditions, and there they may remain for weeks. I have seen such particles of nut more or less covered with mucus swept out of the bowel by a dose of castor oil at least six weeks after the last particle of nut had been swallowed. The concretions thus formed and lodging in the bowel often produce such symptoms as slight local pain and discomfort, slight irregular action of the bowel, slight changes in the appetite with increase of flatulence, and these are often accompanied by a fall in the excretion of urea and a steady and continuous fall in the body weight, often amounting in the course of five or six weeks to as many pounds, or it may be rather more. In such cases the result of the dose of castor oil, sweeping out the concretion and the mucus that has collected round it, is to produce a more or less complete removal of the

previously mentioned dyspeptic symptoms and a steady increase of weight till the normal level is once more reached.

Before I leave the question of gout in the intestines I may mention also that I have seen one case of sprue which, judging from the symptoms, would appear to be a severe intestinal catarrh or gout of the intestines, and this case being looked upon as hopeless and coming to this country merely to die, nevertheless recovered, apparently as a result of the improved conditions produced by a uric-acid-free diet.

A somewhat similar trouble, having, I believe, an exactly similar causation, is that known as hill-diarrhœa, about which there is an interesting note by Dr. P. A. Newton in the *Lancet*, 1904, vol. ii., p. 1417. This, as he shows, is almost certainly due to exposure to cold, especially cold in the early morning hours, in a hot climate; the patient goes to bed when it is very hot and naturally has light coverings over him, and when the temperature falls in the morning he suffers from deficient clothing and, perhaps, before he wakes may have got a chill, especially a chill to the abdomen. The writer mentions that this disease bears in its clinical symptoms a considerable resemblance to sprue, of which we have just been speaking; and he points out that the best preventive is to arrange for sufficient bed clothing so as to guard against morning chill.

Among the symptoms common both to hill-diarrhœa and to sprue he mentions a copious, pale and evil-smelling stool; and I have several times seen stools of this kind in a patient who suffered, as I believe, from intestinal catarrh, due to uric acid and precipitated by cold.

I would also refer to an interesting paper by Dr. H. A. Caley in the *British Medical Journal*, 1906, vol. i., p. 1330, in which he lays very great stress on the relation of colitis to arthritism, gout, rheumatism and rheumatoid arthritis, on the alternation of some of these arthritic symptoms with colitis, and on the fact that eliminants of uric acid, such as alkalies, salicin, and salicylates, may be of service in colitis just as in rheumatic arthritis.

In the same way uric acid pathology enables us to understand the observation made by Lépine,* of Lyons, that opium often increases stomach pain, as it causes excessive acidity and secretion of gastric juice. Opium, as we have seen in previous chapters, increases not only the gastric juice but also the urine, the water from the lungs, and probably all the secretions of the body. Thus

* See *British Medical Journal*, 1901, vol. i., Epitome, p. 48.

Lépine found that the pain was relieved by large doses of sodium bicarbonate, which would diminish the acidity of the gastric juice and also its quantity, as well as that of all the other secretions, and that the pain was also relieved by atropine, which has an action exactly the reverse of that of opium; the opium here acted as a precipitant of uric acid, the alkali and the atropine as solvents.

In the *British Medical Journal*, 1905, vol. i., p. 817, Dr. F. Hare has an article on the hepatic factor in biliousness, in which he attempts to show that the accumulation of glycogen in the liver may cause congestion of that organ and so produce biliousness, and from this he proceeds to explain why starvation, which empties the liver of glycogen, is found useful in cases of biliousness, also why attacks go in series, and that such series are completely broken through by a fever such as enteric. He then proceeds to treat the condition by reducing the carbohydrates so that the liver shall not become congested owing to their excess, and he shows that his treatment is followed by good results.

This appears to me to be a very interesting suggestion, though the real pathology of the condition and the explanation of the results of the treatment are, I believe, different from those which this observer puts forward. As I have already pointed out, the bilious attack or uric acid storm may be greatly relieved by anything that clears the blood of uric acid, because this also lowers the blood pressure.

Now the effect of cutting off the carbohydrates from the diet is in many cases to prevent a more or less troublesome form of dyspepsia which is due to the imperfect digestion and eventual fermentation of starchy food in the stomach and intestines. And it is easy to show that anything that causes gastro-intestinal dyspepsia must also bring about collæmia and further surcharge the blood with uric acid, producing high blood pressure, congestion of the liver and other troubles commonly associated with an attack of migraine. Here we see that the treatment advocated by Dr. Hare does not by any means act in the manner that he suggests, but owes its influence merely to the prevention of dyspepsia and of the collæmia which is secondary to this.

The action of the fever is but one more instance of the same thing; it also prevents bilious attacks by clearing the blood of uric acid, which effect it produces by diminishing the solvent power of the circulation fluids, and most unfortunately of all for Dr. Hare's explanation the bilious attack with high blood pressure, headache, and concomitant congestion of the liver can be absolutely and com-

pletely cured by living on a uric-acid-free diet, which, just like all the other factors here mentioned, clears the blood of uric acid and lowers the blood pressure, and these good results can be brought about without any reference to the fact that such diet often contains a considerable or large amount of carbohydrates, and even if this has not sufficiently demonstrated the facts of the case, the biliousness and congestion of the liver can be brought back at any time by feeding pure uric acid without any regard to or alteration of the carbohydrates in the food. The cure produced, on the other hand, by Dr. Hare's restriction of carbohydrates is of necessity merely a temporary one, for the blood is cleared of uric acid by the uric acid which he is pouring in (a pure meat diet has long been known to do all this) and this condition can only last for a short time and will do no permanent good, for in the end the collæmia, the biliousness, and the congestion of the liver will be worse than before, as the result of the increased introduction of uric acid. On the other hand, the cure produced by a uric-acid-free diet is permanent so long as this diet is continued.

Diagnosis of the dyspepsia, due to collæmia, depends rather on accompanying symptoms than on its own special characters, and where dyspepsia occurs in relation with high blood pressure, slow capillary reflux, headache, fits, or mental depression, asthma, Raynaud's disease, paroxysmal hæmoglobinuria, or Bright's disease, or alternates with gout or rheumatism, as in the case mentioned in chapter viii., there is a strong presumption that collæmia is at least one of the factors in its causation and continuance. It will improve on drugs or diet clearing the blood of uric acid and will be made worse by administration of urates (see figs. 25 to 29).

In the same way gout of the intestines is to be diagnosed from its relation to the taking of metals and drugs which in other circumstances might cause gout of a joint, such as mercury or lead; or the effects of acids, acid salts, cold, &c., as in the cases mentioned.

The indication for treatment in the case of the dyspepsia is to keep the blood free from an excess of uric acid. In the case of gout of the intestine, it is to remove the urate from the irritated part as quickly as possible by means of salicylates.

In both conditions salicylates are extremely useful, and I now often add them to bismuth in conditions where I should formerly have given the latter alone.

The treatment of a bilious attack is the same as that of migraine: first clear the blood of uric acid and then give a course of salicylates to carry it out of the body.

Gout may also affect other fibrous tissues almost within touch of the cæcum, such as those which surround and support the pelvic organs of the female, and salicylate of soda should not be neglected where inflammation of such tissues occurs in a patient who has other evidences of gout or rheumatism, or a family history of these; what has already been said in this and the previous chapter about gout of other similar fibrous tissues should be kept in mind.

In the *Lancet*, 1900, December 15, there is an interesting note of a case of appendicitis, in which "on the third day the bowel symptoms suddenly ceased, and well-marked arthritis of both knee-joints took their place." If all the trouble had been in joints, we should have said this was a well-marked attack of rheumatism with migration from joint to joint; why should we say anything else because the fibrous tissues first affected were those of the cæcum or appendix? In chapter xvii. I have recorded a similar migration from the intestines to the bronchi, or *vice versâ* in my own case.

I think also that gout may account for irritation in the fibrous tissues of one other important organ in the abdomen, namely, the liver, for not only have I noticed that more or less severe pain in the hepatic region is often promptly relieved by salicylates, though this may have been colic and not hepatitis, but in a case under my care at the Metropolitan Hospital, a man with several abscesses in the liver about the size of a walnut (as found at the *post mortem*), salicylates very decidedly relieved his pains and reduced the temperature, thus again directing my attention to the matter.

At the *post mortem* on the above case no suppuration was found elsewhere in the abdomen, and no definite cause for the abscesses; and I notice that Mr. H. J. Waring, in his Erasmus Wilson Lectures at the Royal College of Surgeons, as published in the *Lancet*, 1898, vol. i., p. 621, says that in Dr. Norman Moore's table of thirty-two fatal cases of abscess in the liver "five were apparently primary in the liver (no definite cause being discoverable)."

I also remember to have seen similar pains, apparently in the liver, decidedly relieved by large doses of bicarbonate of soda, which may have acted as the salicylate did.

In this connection also we must bear in mind that the liver is one of the organs which, according to Sir A. Garrod, has a diminished alkalinity and in which uric acid is therefore retained.

And as all introduced uric acid, being absorbed from the gastro-intestinal canal into the portal circulation, must pass through the liver before it can get into the general circulation, and when the alkalinity of the liver is considerably reduced, as at a time of

extensive nitrogenous metabolism with large formation of urea and of the acid products of sulphur and phosphorus previously mentioned, it seems probable that nearly all the introduced uric acid may fail to pass through the liver and be retained there, forming a temporary uric acid filter.

This gives a good explanation of what we find in nature, for if I, having a splendid supply of alkaline salts in my food and blood, swallow some uric acid it will mostly be found in my urine within the twenty-four hours in which it was swallowed, causing a rise in excretion; but if the same amount of uric acid is swallowed by a meat-eater with his high urea and acidity there may be little or no rise in the excretion in his urine for some days after the dose. Meanwhile the absorbed uric acid probably remains in his liver, and a large quantity is thus retained and may give rise, just as in other tissues, to considerable irritation, hypertrophy, congestion and abscess or cirrhosis, according to times and circumstances that condition its stay and other effects.

We can now see that uric acid may not merely produce congestion of the liver indirectly through the venous hyperæmia of an overburdened heart working against high pressure in the arterial systems (see chapter xiv.), but may also directly cause irritation, congestion and hypertrophy, running on in some cases to cirrhosis on the one hand or abscess on the other, and may act on the fibrous tissues of the liver just as it does on fibrous tissues in other parts.

I now cease to wonder that in old flesh-eating days my hepatic region was so constant a focus for pain or discomfort.

In those who go in for the meat and hot water cure of gout or gouty dyspepsia, the blood is kept clear of uric acid by the high acidity; and all the uric acid introduced is no doubt retained in the liver and spleen, so far as these long-suffering organs can find room for it; but that this can be continued indefinitely without more or less serious injury to these organs I am not prepared to believe.

And it is at least possible that wines and spirits produce the evil effects on the liver so commonly credited to them to a large extent indirectly through their effects on acidity and the solubility of uric acid.

It is quite an old and respectable idea that gout and uric acid originated in some defective functioning of the liver, but, so far as I can see, it has no single particle of fact for its foundation. Not only have all my liver troubles cleared up as I got

clear of excess of uric acid, but every single drug that has ever been found useful in these liver conditions either clears the blood of uric acid quickly, like mercury, or more slowly by eliminating it, as the solvents, bicarbonate or salicylate of soda; and all the signs and symptoms that have been supposed to point to liverishness, sluggish or torpid liver, are nothing more than the congestion due either to the direct irritant effects of uric acid on the one hand, or to the slow and defective circulation of collæmia on the other; and the final proof of this is that all such troubles clear up and remain absent when the habit of swallowing unnecessary uric acid has been given up for eighteen months to two years. When people knew nothing either about uric acid or its effects on the capillary circulation they naturally flew to the unknown action of the nerve centres to account for migraine, and to the almost equally unknown action of the liver to account for the formation of uric acid. But all that is now a mere phantom hypothesis, without facts behind it, and both troubles can be completely prevented by keeping uric acid outside the body, yet if they were due to the formation of uric acid inside the body it would be impossible to prevent them. Fortunately, prevention can be effected by anyone, and becomes visible to all in the change of the capillary circulation and blood colouring. With regard to the possible direct causation by uric acid of what is called hepatic colic, it is interesting to notice that Huchard (*British Medical Journal*, 1901, vol. ii., p. 13) has found salicylate of methyl a useful adjunct to other solvents, and I had myself used large doses of bicarbonate of soda in such cases long before I knew anything about its action as a solvent of uric acid. Then my colleague, Dr. C. O. Hawthorne, has a most interesting paper in the *British Medical Journal*, 1901, vol. i., p. 628, which he concludes with these words: "It seems, therefore, that cirrhosis of the liver, even when of the atrophic or multilobular type, must be added to the numerous clinical events capable of producing considerable and indefinitely prolonged pyrexia by a method or agency of unknown nature."

I agree with him as to the clinical observation of facts, but I suggest that the unknown agency is simply that which is in action in gout or rheumatism of other fibrous tissues of the body, and in a number of cases it can be relieved, just as in gout of other tissues, by the use of solvents of uric acid. We are here dealing with gout of the intestines, a precipitation disease, and dyspepsia, which is a collæmic disease, and due to slow and defective circulation in the stomach, liver, &c. But dyspepsia may also be due to slight

local precipitation, and the only rule I can give in treatment is that troubles made worse by precipitants are relieved by solvents and *vice versâ*. A dyspepsia made worse by acid or cold will be relieved by solvents. A dyspepsia associated with collæmia, headache and subnormal temperature will be relieved by precipitants, as acids and tonics; but then we must remember that precipitation troubles may be produced as the collæmic troubles are cured.

The treatment of intestinal putrefaction is the same as that of the migraine or epilepsy which it accompanies (see an abstract by the author in *Brain*, September, 1895, on intestinal putrefaction in certain neuroses).

It is a fact of no little interest that salicylate of soda, which cures all these intestinal pains and colics, will under certain conditions not only fail to cure them, but may produce them when not otherwise present. And these conditions are exactly the same as those in which it also fails to cure rheumatism, or may, as we shall see in chapter xvi. and fig. 71, make the pains worse and raise the temperature.

Now salicylates act best in colic, just as in rheumatism, when the trouble is acute and accompanied by fever; they also act best in the evening and early hours of the night, and least well in the morning hours, and in these, people who are taking salicylates for other troubles may complain of some very decided colicky pains. And these colicky pains while taking salicylates are worse while warm in bed, and are made better by getting up and having a cold bath (see also description of fig. 74).

But we have seen that the colic produced by urates alone without salicylates is made worse by cold and improved by heat, and the pains of rheumatism are, apart from salicylates, made better by heat and worse by cold; but under salicylates they are made better by cold and worse by heat, as we shall see in chapter xvi.

We shall there also see that external warmth acts like a dose of alkali, and increases the alkalinity of the blood, and also that salicylates act best when the alkalinity of the blood is low, and may not act at all, or even do harm, when it is high.

And the fact that such colic is made better by warmth apart from salicylate, and worse by warmth conjoined with salicylates, shows that it is absolutely dependent upon the solubility of uric acid in the blood, and is made worse by anything which interferes with that solubility and better by anything which aids it.

Now, apart from salicylates, external warmth raises the alka-

linity of the blood and increases the solubility of uric acid; it therefore does good in colic; but when salicylates are in circulation, warmth, which raises the alkalinity of the blood, hinders the solvent action of these substances for uric acid, and therefore makes the colic worse.

I will not go into this matter, except to point out its bearing on treatment, but must refer to what I have already said in chapter ii. on fig. 8, and in chapter ix., and shall have to say in chapter xvi.

Now it is obvious that if salicylates are not good solvents of uric acid when the alkalinity of the blood is high, they may fail to relieve colic, such as that produced by lead, when it has lasted some time, and has consequently greatly lowered urea and acidity of urine, and raised to a corresponding extent the alkalinity of the blood, and that in such conditions their action will be aided by giving them with ammonia, which raises the acidity of the urine, or in alternate doses with acids or salts, which raise the acidity.

It follows also that when we are trying to cure colic with salicylates, and have got the patients well under their influence, we must not go on with the application of hot poultices or fomentations to the seat of pain.

Much more also does it follow that we must never expect the best action of salicylates in colic, or, for that matter, in rheumatism either, if we persist in giving them along with the alkaline salts of potash or soda, and, indeed, the satisfactory action of salicylates in acute rheumatism and their very doubtful benefit in the chronic disease are probably entirely due to the different reaction of the blood in these two conditions.

In the treatment of typhlitis or appendicitis in cases where suppuration has not already taken place, I give salicylates as for arthritis and judge by the results. The best way is to give salicylate or aspirin much as for acute rheumatism, and to apply a local icebag or cold in other form, and under no circumstances to use local heat unless we wish the salicylates to do harm.

If the drug clearly controls the pain and temperature and repeats this result on any slight sign of a subsequent relapse, I advise the patient to go on taking this drug for some time, and to keep it constantly at hand in case of need, and then to slowly alter diet so as to clear the body and blood of all excess of uric acid.

But if diet cannot be altered they are almost certain to have a

relapse (for gout tends to go on recurring in the affected tissues, which act the part of the uric acid filter), and they had better arrange to have the appendix removed as the surgeons advise, though I see from a statement in the *Lancet*, 1900, vol. i., p. 646, that this does not always put an end to the trouble, for if any of the irritated fibrous tissues are left the gout will recur, and those who are full of urates may have it in other parts of the intestines or in the stomach; and no one, I think, now removes the great toe for gout. When suppuration has taken place, salicylates and diet are too late, and the patient must be treated on ordinary surgical principles for the local troubles.

I notice with interest that Mr. Arbuthnot Lane says in the *British Medical Journal*, 1905, vol. i., p. 702, "That the operation of removal of the appendix not infrequently fails to relieve patients of their painful symptoms is well known to all of us, and no amount of statistics pointing to a contrary conclusion to this can be relied upon." I give this quotation as further evidence of what I have just said, *i.e.*, that if the trouble is due to gout of the intestines it is obvious that it may recur and recur so long as there is any fibrous tissue left. The surgeons are here removing not the cause but the consequence, and if space permitted I could give records of quite a number of cases in which removing the cause has rendered all resort to operation unnecessary.

In the dyspepsia and slight colicky pains produced by urates or by urates and salicylates together, there is generally a little rise of temperature, say to 99° F. or 100° F., and I have several times noticed in children who are taking salicylates, for a cold perhaps, that the temperature is raised to this extent in the early morning hours, but falls to normal when the drug is left off; no doubt in these cases salicylates and alkalies are causing in the morning hours, when their actions clash, some little gouty irritation somewhere which suffices to raise the temperature to this extent.

With regard to the cause and cure of gout of the intestines by diet, there is an interesting note in the Epitome of the *British Medical Journal*, 1901, vol. i., p. 65, on a communication from the physician to the French Legation at Pekin, who points out the rarity of appendicitis among the Chinese, and the absence of meat from their diet. Credit is given to the diet for keeping the bowels open; but I should consider that in relative freedom from uric acid it had a still more important quality.

In the *Lancet*, 1905, vol. i., p. 372, is an annotation on the prevention and cause of appendicitis, in which it is pointed out

that this disease is nearly four times as common in men as in women, and looking upon it as gout of the intestines it is perhaps not without interest to remark that this is also the case with gout. We may also do well to bear in mind the way in which dysentery is cured by a simple diet of white of egg and other uric-acid-free substances, and the apparently heavy mortality which occurs in this disease when it is treated with meat juices and extracts and other substances containing xanthin.

No doubt the latter foods would serve to increase the intestinal irritation and catarrh, while the uric-acid-free foods would allow the irritation to die out.

Similar records appeared during the Russo-Japanese war. We recall the remarkable manner in which Chinese, Japanese, and other vegetable feeders recovered from such troubles as dysentery by a simple unstimulating diet, while those fed on strengthening food—beef tea and meat juices—either failed to recover or took much longer.

I am often asked whether gall-stones have any relation to uric acid, and the answer must be in the negative. There is no direct connection between uric acid and gall-stones, yet there is a very interesting indirect connection which I mention here, not because gall-stones are connected with gout, but because they have an anatomical relation to the intestines. Gall-stones may be related to collæmia, so that they stand in the opposite group to gout. They occur more often in women and are most commonly seen at or after the age of fifty.

The effect of collæmia is to render scanty and concentrated all the secretions and the excretions of the body. In severe collæmia the saliva is thick and sticky and the mouth almost dry, the excretion of water from the lungs is diminished, the water from the kidneys is also diminished, so that the urine is thick and readily throws down deposits of salts. Collæmia is a universal condition, and there is no reason to doubt that when all the excretions are scanty the bile is also scanty. Just as we see that the saliva tends to throw down tartar, so also does the bile tend to throw out mucus and pigment which form the commencement of a gall-stone; and no doubt each time the collæmic condition comes into force throughout the body, not only will further quantities of mucus and pigment be thrown out, but various other insoluble substances from the bile will also be deposited and collected on the gall-stone beginning to form. We are now in a position to explain the relation of gall-stones to age and sex, for both these factors have an

important influence on the causation of collæmia, with regard to which those who have studied the previous chapter on uric acid metabolism will understand how it comes about that there is more uric acid in the blood and consequently more likelihood of collæmia about the decline of life from fifty years onwards. Hence it is that I regard it as no mere accident that it is about this time of life that gall-stones are most common, for we must remember that gall-stones probably take some time to form, and that though they come into prominence at fifty the original mucus of such stones was probably laid down some years previously. But those who suffer from collæmia more markedly at fifty have in all probability been suffering from it from time to time and more or less seriously for some years before fifty.

And then as to sex and the great preponderance of gall-stones in women we have two factors, one the somewhat inactive lives some of them live, and inactivity must in some degree mean a deficient circulation, change and movement in all the interstitial fluids of the body; hence, other things equal, those fluids tend to throw down deposits of mucus, pigment and salts, especially in those who are sedentary; and the other factor is that referred to in chapter iv.—the fact that women have a well-marked cause of collæmia for a certain number of days in every month, while a man of the same age may steadily go on storing uric acid for some years and not have collæmia at all, even for a few hours. This, it will be remembered, as we shall further see in chapter xv., gives the explanation of the fact that women rarely have gout till about fifty, as their monthly collæmia prevents the accumulation of uric acid in the body, but as we now understand this will not prevent, but on the contrary greatly facilitate, those changes in the condition of bile which lead to the formation of gall-stones, and of the saliva, which lead to deposits of tartar, and undoubtedly the latter deposit tends to cease on the adoption of the uric-acid-free diet.

CHAPTER XI.

Raynaud's Disease.

Just as we have seen in the previous chapter that the defective circulation in the gastro-intestinal mucous membranes produced by uric acid may account for many of the phenomena of dyspepsia, there is good reason to believe that the defective circulation in the skin and extremities similarly produced will account for the production of Raynaud's disease.

The defective circulation is indeed common to the whole body, but the skin and extremities are specially affected, because, as Raynaud points out, they are the parts of the body which are most exposed to loss of temperature, and because, as we have seen in chapter v., cold is itself a powerful contributing factor in the causation of collæmia, and the extremities have a larger surface, in proportion to bulk, than any other part of the body.

It may be said that Raynaud in his "Thesis," published in 1862, attributed the local asphyxia and symmetrical gangrene of the extremities which he described to a spasmodic contraction of capillary vessels.

He acknowledged that this might be a general condition, affecting the vessels all over the body at the same time, but producing serious effects only in the extremities, because these are the portions of the body which have most surface in proportion to bulk, and therefore most quickly lose their heat by conduction and radiation, and most early become cooled down below the point at which the life of the tissues can be continued ("Thesis," p. 166). He observed that at the time of an attack of asphyxia or gangrene of the extremities, the skin was everywhere cold and pale, and a case of which I shall give notes shows that the temperature of the body at a distance from the seat of attack falls at the time of an attack, and rises again as it passes off; bear in mind also fig. 5.

I shall also point out that there is good reason to believe that the

vessels of the kidney are obstructed at the same time with those of the skin, and Raynaud himself mentions the signs of this without understanding their import; and there is also, as we have seen, reason to believe that the vessels in the brain, lungs, and other viscera are in a similar condition.

Raynaud himself, however, gives no good or satisfactory reason why the arterioles and capillaries should be affected by this spasmodic contraction; it is true, he remarks, that it is often met with in nervous people and in those who suffer from hysteria, epilepsy, &c.; but what influence he attributes to the nervous system in producing these phenomena all over the body is not very clear.

At this point my researches come in, and I have suggested that the vessels are obstructed owing to the presence of uric acid in the circulation (*British Medical Journal*, February, 1889, p. 191); and this obstruction we can now measure with accuracy, and, as has been seen in chapter v., it was Raynaud's observation that led me to measure it in the skin.

I will now give notes of some cases, and then discuss Raynaud's cases and arguments.

Margaret C., aged 3 years, came among my out-patients, September 23, 1889. Her mother said that some of the toes of both feet were cold and blue and the child complained of pain in them. The right foot was seen to be blue-black, cold, and tender as far as the middle of the metatarsal bones, the left foot had the second, third, and fourth toes blue-black and cold, and the colour extended in lines a little into the sole of the foot. Second sound of heart relatively loud. Pulse irregular with marked plus tension. Had measles twelve months ago, and pertussis at the same time. Had not had any fever lately. Has three sisters who are all well.

Father subject to gout, his family also subject to it and to phthisis. Mother well.

The feet were wrapped in wool and a quarter of a tabella of nitro-glycerine given frequently, and she was admitted.

September 24.—Much better. Feet are hot and a little tender, but the colour and coldness have both gone. Pulse 120: heart, first sound rather weak, second sound relatively loud. Urine of the attack yesterday gives a uric acid urea relation 1—8·3, an enormous excess of uric acid, but there is no albuminuria. Given a little dilute nitro-hydrochloric acid and ɱi. of tinct. opii twice a day.

September 26.—Going on well; urine of this day gives a relation of uric acid to urea 1—20·7.

September 27.—Another attack in the evening, the left foot being most affected; it was blue as far as the ankle. In the right foot only two or three toes were blue, just the reverse of the previous attack. Was again given nitro-glycerine. Urine of the attack (probably a mixture) gave uric acid urea relation 1—22. Urine later on, after all the nitro-glycerine had been given, 1—53. The first lot of urine was a considerable quantity, 450 cc., and probably included urine before as well as during the attack; hence the relatively small amount of uric acid—1—22—as compared to 1—8 in first attack. The great effect of nitro-glycerine on the excretion is well shown in the relation of 1—53, which is in marked contrast with 1—22. We can now see that the second attack on September 27 was a rebound from the retentive effects of the nitrites, acids and opium given for the first attack; they should have been followed by salicylates.

September 28.—Nearly all right again and only a few scattered petechiæ and some œdema marked the parts of the feet affected yesterday.

It was now noticed that there was some peeling on the hands and chest, and, thinking that she might have had scarlet fever, she was sent out.

Her mother denied that she had had any rash or sore throat previous to admission, and I saw her a few days later at her own home, and examined her sister, who showed no signs of peeling.

Eliza H., aged 6. Admitted into the Royal Hospital for Children and Women, November 27, 1890.

Her family have always lived in London. There are three brothers and sisters younger, and one older than the patient. Mother has had nine children born alive, no miscarriages.

Mother is subject to cough.

Mother's mother and mother's brother had rheumatic fever.

Father's mother had "chalk gout."

No ague in family.

Patient had measles and bronchitis when fifteen months old, and whooping-cough at 4 years old.

Eyelids and face generally very pale and puffy. Has conjunctivitis and opacity of corneæ.

On admission—pulse 120, temperature 100° F, respiration 24.

Soon after admission she passed some urine which was almost black, threw down a grumous deposit, and contained a large amount of albumin. A few hours later it was the colour of dark sherry, and later still, quite normal.

December 1.—Urine to-day amber, clear, acid, 1018. Phosphates. No albumin. I examined her heart and found reduplication of the first sound between the apex and the left border of the sternum, and a loud second sound both at apex and base.

Pulse quick, 80 to 105, irregular in force and time; and it was difficult to judge by the finger as to the tension, but pulse tracings showed at times considerable tension. When the pulse was quick there was probably some failure of the heart, and tension was not well maintained on this account.

Spleen dulness normal.

The urine of November 28 was port-wine coloured, with a grumous sediment, 1018. Contained a very large amount of albumin (about 10 or 12 parts per 1,000, Esbach). Gave hæmoglobin lines with the spectroscope, and a relation of uric acid to urea of 1—30.

December 2.—"The child's hands were washed with cold water at 6 a.m. After this she was well till 1 p.m., when she began to complain of pain in the hands, which were seen to be quite blue up to the level of the wrist. This blueness persisted up to 1.10 p.m., when the colour only remained beneath the finger-nails; the rest of the hands were red, puffy, and markedly swollen, but quite cold; the puffiness and redness gradually faded, and at 2.30 p.m. the hands were normal in appearance and temperature. Pulse 80, no marked plus tension during the stage of blueness and congestion. Heart first sound prolonged, second sound accentuated at apex and base. The child had marked pallor, and appeared to have intense headache during the attack in the hands, but said she did not know what was the matter, and had no headache. At 2.30 p.m. she sat up and began to play with her toys.

"Blood drawn from finger as congestion stage was passing off showed marked excess of white cells, which were actively motile and putting out many processes. Red corpuscles formed bad rouleaux, and scattered among them were collections of bright refracting nuclei about the size of one-sixth of a red cell, and it appeared as if in places the cells had burst and discharged their contents." I am indebted for the above description of an attack and the condition of the blood to the notes of my colleague, Dr. S. W. Wheaton, who was then Registrar.

December 4.—Urine of twenty-four hours, ending this morning, during which there was no attack, was 19 ozs., amber, smoky, turbid, 1020, faintly acid. No albumin, some phosphates, uric acid, urea relation 1—17.

Had attacks of local asphyxia in hands or feet, or both, on December 6, 7, 8, 9. On the 11th and 12th there were no attacks, in spite of her hands being washed in cold water as before. The above attacks lasted from ten to forty minutes, and attention was directed to them by the child complaining of pain in the affected members. They were not accompanied by any marked rise of temperature, or followed by hæmoglobinuria, in fact, the temperature was subnormal all the time.

December 13.—Urine of twenty-four hours, ending 8 a.m. to-day, 24 ozs., pale amber, turbid, neutral, 1016. Urea 1·2 per cent.; uric acid, 0·04704 per cent. Relation, 1—25. Weight, 38 lbs. Urea, 3·5 grs. per pound, which, for a child of her age, is very low, and shows failure of nutrition.

Had a slight attack in the right hand at 7.15 this morning, lasting ten minutes.

December 15.—Urine of twenty-four hours, 25 ozs., pale amber, slightly acid, 1019. Urea 1·4 per cent.; uric acid, 0·05712 per cent. Relation 1—25.

Urea still very low. She is on farinaceous diet, and sister says she is always very hungry (had she been starved?). I ordered her to have meat and be fed up.* No doubt this low nutrition and relative excess of uric acid is the cause of all her trouble.

December 16.—Had four distinct attacks in hands and feet, first at 11.25 a.m., second, 4.25 p.m.; third, 4.50 p.m.; and fourth, 5.30 p.m. Urine passed between 9 and 11 a.m. to-day, 2½ ozs., amber, turbid, neutral, 1025. Uric acid urea relation, 1—19.

Urine 11 a.m. to 1 p.m. (being a mixture of the urine corresponding to the attack of 11.25 a.m., lasting twenty minutes, with the urine of the remaining one hour and forty minutes free from attack), 1026, faintly acid; uric acid to urea, 1—23.

There was thus apparently less uric acid at the time of the attack than before it; but as I have pointed out in the case of headache, epilepsy, and other paroxysmal effects of uric acid, there is a variation in the excretion in both directions, a plus excretion during the attack, and a minus before or after it, or both; and when the separation is not accurate, as in slight attacks it can rarely be, the minus excretion before or after the attack more than balances the plus excretion during the attack (which only lasted twenty

* I did not at this time know that meat directly introduced uric acid into the body, or I should not have ordered it, and no doubt this partly accounted for the continued excess of this substance in the urine.

minutes out of two hours urine); and we get the result here shown, namely, that there was a greater excretion in the two hours before the attack than in the two hours including the attack; in both periods, however, there was a considerable excess of uric acid, and the urine is, after all, but an imperfect index of the amount of uric acid in the blood (see chapter iii.).

December 19.—Had no attack on the 17th and 18th. To-day she had an attack at 1.50, lasting only ten minutes, but followed by a rise of temperature to 102·8° F., and the urine passed next after this at 5 p.m. contained hæmoglobin.

Urine passed at 1 p.m., before the attack, pale amber, slightly acid, 1026; uric acid to urea 1—21.

Urine passed at 5 p.m. (the first after attack), grumous red-brown, with powdery sediment, strongly acid, 1030. Hæmoglobin lines. Much albumin, but part of the turbidity clears with heat (? urates). Uric acid urea relation, 1—22. Total urea in 100 cc. was 49 grs. Total uric acid, 2·2 grs. Total acidity reckoned as oxalic acid, 5·8 grs. Relation of acidity to urea, 1—8·4, that is to say, acidity was low, and with a low acidity we had a large excretion of uric acid, 1—22. But I said above the urine was strongly acid; how then, it may be asked, was the acidity low? I reply that the urine (as is generally the case with excess of uric acid in the blood) was a very concentrated one, and the excretion of water small; hence the apparent acidity was high; but when we came to reckon the total acidity by the side of the total urea or the hourly excretion of acid in grains, we find that the acidity is relatively low, for we only find 1 gr. of oxalic acid for 8·4 grs. of urea, whereas my researches show that taken over a long period of time, the relation of acidity to urea is 1—6·8, 1 gr. of oxalic acid for every 6·8 grs. of urea, whereas here we only got 1 gr. for 8·4 grs. of urea, so that, as I have said, acidity is really low, though estimated only with a piece of litmus paper it would appear high. Such is the difference between exact and inexact investigation.

What really happened in the attack of hæmoglobinuria was, probably, as follows: At the time of the local asphyxia, 1.50 p.m., there was intense collæmia, and an enormous excretion of uric acid in the urine, having the relation, say, 1—8 or 1—12, but in this case the attack only lasted for ten minutes, and the excessive excretion only went on probably for half an hour, but we unfortunately got no urine passed till 5 p.m., nearly three hours later. Meanwhile the temperature has risen, the alkalinity of

the blood has diminished, the excretion of uric acid has fallen greatly, possibly down to 1—40 or 1—50, showing that there is no longer any excess of it in the blood, and the acidity of the urine has risen (it was possibly alkaline at the time of the attack) but the blood has been flooded with hæmoglobin, and this slowly finds its way out of the kidney; the result is that in the urine passed at 5 p.m. we have plenty of hæmoglobin, a low acidity, a large excretion of uric acid, 1—22, though this, in all probability, was the product of a mixture of the very much larger excretion during the attack with the very much smaller in the two and a half hours that followed it, so that the relation of uric acid is reduced from 1—8 to 1—22; just as the acidity is a mixture of the alkaline urine of the attack with the highly acid urine of the two and a half hours following it, when with high temperature there would certainly be a rise of urinary acidity and a corresponding fall in the alkalinity of the blood.

Now that I have gone into these matters at length, I shall not require to repeat the explanation of the same phenomena in subsequent attacks.

Dr. Wheaton examined the blood one hour before an attack, and found 3,800,000 red cells per cubic millimetre; he again examined it one hour after an attack, during hæmoglobinuria, and found 2,990,000 cells only, a very great diminution. He repeated the examination on two subsequent occasions with similar results; and also found that the blood after the attack showed increase of white cells, and increase of coagulability.

December 20.—She had an attack of local asphyxia in both feet, lasting from 6.55 to 7.30 and followed by a rise of temperature to 99·8° F. The urine passed after this, at 8 p.m., contained hæmoglobin.

Some urine passed before (? how long) the attack gave a relation of uric acid to urea 1—28, and that passed at 8 p.m., containing hæmoglobin, gave a relation 1—30. Here there was probably an admixture of the excretion of before or after with that of during the attack, but as I was unable to obtain definite information as to the hour at which the specimen before the attack was passed, no valid conclusion can be drawn from my results. I got many such results from the uric acid headache before I found out the importance of separating carefully the urine of the attack.

December 23.—Local asphyxia in the toes of both feet 3.20 to 3.35 p.m., or lasting slightly till 4 p.m. Urine passed during

the attack of a pale port-wine colour (a mixture of before and during), slightly turbid, alkaline, 1022; uric acid to urea 1—23.

Urine drawn by catheter at 4 p.m. (the end of the attack, excretion of about half an hour) dark port-wine colour, brownish deposit, slightly acid; uric acid to urea 1—28.

The remarks I made before about the effects of admixture apply here, but we see that there is less uric acid with the hæmoglobinuria near the end of the attack.

On December 21 she passed some hæmoglobin at 6.15 p.m., again on the 24th at 1 p.m. and on the 25th at 9.30 a.m.; in none of these cases was the passage of the hæmoglobin apparently preceded by local asphyxia; possibly the attack escaped observation; the child was very heavy and dull in the attacks, and if other children were making a noise, her first cry of pain might not have been heard. Later on, December 25, however, 5.15 p.m., both feet were affected, and remained so for about an hour, and the urine passed at 6 p.m. contained hæmoglobin, as also the specimen next passed at 6.15 a.m. on the 26th, but that at 9 a.m. on the 26th was clear.

December 28.—She had an attack in which the left foot led the way, and was followed by the right 5.15 to 7.30 p.m.

December 29.—The hands and feet were both affected, 5 p.m. to 6 p.m., and the temperature rose to 100·8° F., but the attack was not followed by hæmoglobinuria.

December 30.—The hands and feet were affected, 3 to 3.45 p.m., and again 5 to 8.30 p.m. The urine passed at 8.30 p.m. contained hæmoglobin, and that at 9.30 the same.

I did not estimate the uric acid urea relations in any of these specimens, because the separation was not sufficiently accurate to make it worth while; the attacks were slight, lasting a few minutes to half an hour, and in no single instance was the urine corresponding to the attack obtained separately.

In the previous more severe case of Raynaud's disease, where an attack lasted nearly twenty-four hours, there was much less difficulty about obtaining the excretions corresponding to the attack, which gave a relation of 1—8. That is, with the more severe and prolonged attack there was a greater and more continuous excess of uric acid in the blood and urine.

December 31.—Hands and feet affected, 5.15 to 7.30 p.m.

1891. January 4.—Left hand affected, 3.25 to 4.10 p.m.

January 5.—Hands and feet affected, 9.30 to 10.45 p.m.

Right hand affected, 1.5 to 1.30 p.m.

January 6.—Hands affected, 1.30 to 2.30 p.m., and temperature rose to 99·4° F.

,, 7.—Hands affected, 9.50 to 10.10 p.m.
Right hand affected, 5.10 to 5.35 p.m.
Both feet ,, 6.45 ,, 7.15 ,,

,, 9.— ,, ,, ,, 6.45 ,, 7.45 ,,

,, 11.—Both hands ,, 6.5 ,, 6.25 ,,

January 15.—I examined the urine of twenty hours ending 2 p.m. to-day, 18 oz.; specific gravity 1018, and found: Urea, 1·7 per cent.; uric acid, 0·06384 per cent.; total urea, 161 grs.; uric acid, 5·2 grs.; acidity, 15·7 grs.; uric acid to urea, 1—27; acidity to urea, 1 to 9. This shows that urea is still very low per pound of body weight for a child, uric acid is high and acidity low, hence recurrent excess of uric acid in the blood, which is the cause of the trouble.

She is up and going about, but seems dull and cross. Eyes still very bad.

January 17.—Feet affected, 12.5 to 12.45 p.m.

,, 18.—Both hands affected, 10.30 to 11.15 a.m.
Left hand affected, 5.30 to 6.30 p.m.

,, 19.—Feet and hands affected, 5.45 to 6.30 a.m.
Right hand affected, 5.10 to 6 p.m.

,, 20. ,, ,, 6 to 7.15 a.m.
,, ,, 11 to 11.30 a.m.

,, 22.—Left hand affected, 5.40 to 6.15 p.m.

On this day, as the attacks seemed to be pretty frequent, I determined to treat the uric acid, and she was accordingly put on salicylate of soda gr. viii. three times a day after meals, and had the first dose on the evening of January 22, after the forty-second attack of asphyxia. She was also given a small dose of acid and strychnine three times a day to aid the action of the salicylate.

From this she went for twenty days right off without any attack whatever, her forty-third attack of local asphyxia occurring at 2 p.m. on February 11, while out on the roof of the hospital.

January 29.—Better and more cheerful, and all the nurses bear witness to the improvement in her temper, though her eyes are still bad.

February 5.—Still no attack, and temper continues to improve. Yesterday, however, the temperature rose to 101° F. at 10 p.m., but there was no sign of an attack in limbs or urine.

February 11.—Attack while on roof at 2 p.m., part affected not stated.

February 13.—Feet and hands affected 11 a.m. to 1.30 p.m. Was out on the roof early in the morning.

February 14.—Seems well in herself, and is singing away; salicylate mixture to be given four times a day.

February 19.—No attacks; has been on the roof twice for about an hour each time. Going on well.

February 22.—She had her forty-fifth and last attack in both ears from 7 to 8.30 a.m., and it is noted that her temper was very bad at the time of the attack.

February 23.—Temper is much better now than before salicylate was begun.

March 5.—Still no attacks in spite of exposure on the roof in the cold of the morning at 7 a.m. All drugs left off to-day.

She was on the roof on February 17, 18, 25 and 27 without any effect being produced.

March 9.—Weather very cold with a strong east wind, so salicylate was resumed again.

March 12.—Was on the roof at 7 a.m. to-day. Thermometer 27° F. No effect.

She now went on well, her temper keeping placid, and she seemed bright and happy in spite of the condition of the eyes, which remain so bad that she can only see indistinctly, and is afraid to walk or run by herself.

May 7.—Well in herself now, but had an attack of tonsillitis about two weeks ago, for which, as another child in the ward had diphtheria, she was isolated; she, however, got quite well, and had no sequelæ.

About a week ago I put her on small doses of liq. calcii chlor. with a view of trying whether I could produce some retention of uric acid, and then, by bringing it out into the blood again produce an attack. I therefore examined the urine of twenty-four hours ending this morning, and found total urea 187 grs., uric acid 7 grs. Relation 1—26. Acidity was still low, but urea had risen somewhat in accordance with the improvement in the child's general condition, being now about 4·6 grs. to the pound. It seemed, however, that with this continued low acidity I was not likely to produce much retention of uric acid, and I therefore gave up the attempt and sent the child home.

June 22.—She still attends as an out-patient; is cheerful and well, getting fat, and has had no attack of any sort.

She had thus altogether 45 attacks of local asphyxia and 9 of hæmoglobinuria; 42 out of the 45 attacks occurred in 52 days

from December 2, 1890, to January 22, 1891, and 3 attacks in 31 days, from January 23 to February 22, 1891. In the week ending January 22, the day on which salicylates were begun, she had 8 attacks, and then she went 20 days without an attack at all; then came 3 attacks in the next 11 days, and after that none, in spite of cold weather (as our winter certainly did not end on February 22) and exposure on the roof as before.

The points of interest to me are the pallor and headache, which occurred during an attack, as described by Dr. Wheaton; the fact that her temper was generally bad, and was worse in the attacks; that it improved when salicylates were given to such a marked extent as to be noticed by all who saw her, and that the attacks diminished after the salicylate, which no doubt cleared out much uric acid.

Washing her hands in cold water or exposure to cold on the roof of the hospital seemed on several occasions, till she came under the influence of salicylates, to precipitate attacks, and this is of some interest from the point of view of the causation of obstruction of capillaries by colloid uric acid (see p. 168). For local cold may increase locally the precipitation of colloid uric acid, and this will be more serious the greater the cold and the greater the amount of uric acid in the circulation available for local precipitation. When an attack followed some hours after exposure to cold, it is possible that the hands never recovered their warmth and that some amount of precipitation was going on the whole time. Dr. Wheaton's observation of increased coagulability of the blood is also interesting, as the presence of colloid uric acid might to some extent account for this (see Causation of Thrombosis in chapter xii.).

The case also illustrates the fact observed by others, that the attacks are generally in the morning; and this corresponds with the well-known fact that the greatest excretion of uric acid in the urine, and probably the greatest collæmia, occurs in the alkaline tide of the morning; and in the morning also we are most likely to meet with that combination of urates with phosphates and alkaline salts which may induce the colloid state.

Dr. Wheaton says that the pulse during an attack was 80, and showed no marked plus tension.

But 80 is a somewhat slow pulse for a child of 6 years. The quickest pulse on her charts is 141, and the slowest 54, and pulses of 60, 64, and 72 on several occasions corresponded with attacks.

As to tension, I found that it was very difficult to estimate by the finger in this case; but some tracings I obtained show consider-

able tension, though the pulse rate was above 80 (see *Transactions of the Medical Society*, vol. xv., p. 155, where reproductions of these tracings will be found).

Again, when her pulse was quick it was not always because the tension was low, for there were several signs of heart failure here, and, as I know from observations on other cases, when the heart fails in its efforts to force the capillaries, which are obstructed, its systoles become imperfect (as some of my tracings from this case show) and its action quick; and Marey's law that pulse rate is inversely as arterial tension, or that the length of the ventricular systole is directly proportional to the amount of arterial resistance, holds only so long as the heart is equal to its work; and when the systoles become imperfect and the heart quickens, tension is not well maintained in spite of great obstruction of capillaries. "A long pulse means a labouring heart,"* but a short pulse with peripheral resistance and slow capillary reflux means a failing and dilating heart.

Hannah E., aged 47, admitted into the Metropolitan Hospital, April 7, 1892.

Had one child, which died at the age of five months, of "pulmonary consumption."

Has two sisters, who are well.

Had five brothers, but one is dead, and one dying of consumption; three are well.

Father died of apoplexy.

Mother, aged 66, is well.

Patient had rheumatic fever twelve years ago; phlebitis of right leg ten years ago; inflammation of lungs eight years ago; bronchitis twice since that.

Fingers have been painful and blue, with tendency to ulceration, on and off for three years.

The right hand was first affected and the left became affected in December, 1891, when she had bronchitis.

The first symptom was pallor or blueness of one or more fingers, especially after washing the hands in cold water. Later on, blebs formed on the fingers and burst.

Fingers are growing shorter and more stumpy, and getting more painful.

Has general shivering when the attacks of coldness come on in the fingers.

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* Mahomed, *Guy's Hospital Reports*, 1879.

A pale, poorly nourished woman.

Temperature generally subnormal ; pulse 80, irregular in force.

Heart.—Apex-beat in fifth space, just outside the left nipple line. Blowing systolic murmur at the apex. Other sounds, nothing remarkable.

Lungs.—A few mucous râles both sides ; no dulness.

Abdomen.—Nothing abnormal. Bowels tend to be constipated.

Urine.—Specific gravity, 1012 ; contains a trace of albumin. Thinks she has been passing more water of late.

Legs show dilated venous capillaries.

Right hand.—All fingers somewhat blue and shining, but the first and middle fingers have a red tinge and are somewhat clubbed, while the ring and little fingers are tapering and somewhat colder than the others.

Nails on the first and middle fingers are short and have transverse striæ, the others have longitudinal striæ.

All the fingers are marked with scars, which have dried up, and all are more or less painful.

Left hand.—All fingers are blue and shine, and taper from the first interphalangeal joint to the tip. All are abnormally cold and rather tender.

On the index finger there is an excoriation just in front of the nail, where a slough has separated.

The middle finger has a suppurating point under the nail, and on the last phalanx there is a bleb the size of a filbert, containing dark fluid and a slough, very painful.

The ring and little fingers are tapering and cold.

All nails are curved and longitudinally striated.

Sensation is fairly perfect in all fingers.

The urine was examined on several occasions, and it always contained a trace of albumin, and had a low specific gravity.

I concluded that we were dealing with chronic Bright's disease and chronic bronchitis, dilatation and hypertrophy of the left ventricle, with or without some lesion (rheumatic) of the mitral valve, with, at the present time, some failure of compensation, shown by the irregular force of the systoles and the somewhat rapid rate of action ; and that with these conditions it was not very extraordinary that we should find what we may call chronic Raynaud's disease, with exacerbations affecting the hands. Here we have in fact, exactly that condition which causes women to suffer from Raynaud's disease more than men, and which, I shall have also to suggest further on, may be the cause of their more frequently suffering from chorea, namely, weakness of the heart muscle.

It is interesting to note the history of rheumatism and thrombosis as pointing to excess of uric acid, first in the joints and then in the blood; and that her first attack of Raynaud's disease came on when she had bronchitis, with the collæmia of dyspnœa (see chapter v.), and probably some increase of the heart failure.

April 7.—I put the patient on nitro-hydrochloric acid and nux vomica three times a day before meals, and salicylate of soda three times a day after meals, and ordered a tablet of nitro-glycerine B.P. from time to time when the fingers were more than usually painful.

April 12.—Still has attacks of pain in the fingers, which turn white and blue and get very cold. The pain in them wakes her up. Takes the nitro-glycerine tabloids and is sure they do good; feels warmth and comfort returning to fingers about three-quarters of an hour after one.

April 13.—Pains relieved by the nitro-glycerine. Temperature to be taken before and after a tabloid.

April 14.—Complains of coldness of left foot, the great, second and third toes being painful and rather blue.

April 16.—Temperature in axilla ·6° up after a tabloid had relieved the pains. Observation to be repeated.

April 19.—Better; no attacks at all. No tabloids taken; fingers are less cold.

April 20.—Had an attack with a headache at 7.30 a.m. to-day. A tabloid was given at 8 a.m., and a second soon after. Got quickly better after the second tabloid. Temperature in the axilla at the time of the attack was 97·2° F.; when the tabloids had relieved the fingers it was 97·8° F., and it rose to 98·2 in the evening.

April 27.—No attacks for several days; the slough on second finger of left hand has separated and the ulcer is healing.

May 3.—Has a headache to-day, and the fingers are colder; they were fairly warm yesterday.

May 4.—Above mixtures left off, and phosphate of soda ʒss. given three times a day in their place.

May 7.—Has an occasional headache, but the fingers are only slightly affected; no severe attacks of late.

May 9.—Had a bad headache at 11 a.m. to-day.

May 11.—Fingers very blue and cold to-day in spite of the warm weather.

May 14.—Fingers are much less blue to-day.

May 17.—Had a bad headache at 2 a.m., and the fingers are worse to-day. The index finger of the right hand is getting swollen and painful in the last phalanx. After this she soon got better and went out.

The temperature was generally subnormal, the highest being 99·2° F. on the evenings of April 20 and 27, and the lowest 96·6° F. on morning of April 8.

Of Raynaud's twenty-five cases, twenty were women ; they were for the most part young, only one being (48) older than this patient. And it is just in young women, as we shall see in the next chapter, that we get most collæmia.

One of his cases, No. 18, had mitral disease (constriction). This patient was worse in the spring of the year, and Raynaud mentions the autumn and spring as being common seasons of onset.

Spring is the season for the large excretion of uric acid for the year, but there is also sometimes a large excretion in the autumn, well known to sufferers from headache ; it is a rebound from the high nutrition of the summer holiday.

This case also fulfils Raynaud's definition in that the troubles were to a large extent symmetrical; and like it, also, several of his cases became chronic, lasting for years, with periods of intermission—a condition of things which he thinks is specially seen among the slighter forms of the trouble.

In the case I have just narrated above I did not estimate the uric acid because her attacks were not very well marked, so that it would have been difficult to separate the urine corresponding to them.

Eliza H. had hæmoglobinuria with some of her attacks, and I shall give presently the amount of uric acid I found in the urine in other cases of hæmoglobinuria. This patient also had pallor of skin, headache, and bad temper at the time of her attacks ; and when she was put on drugs similar to those I gave to Hannah E. her symptoms diminished in severity or disappeared.

In the case of Hannah E. the family history is of interest, for her father died of apoplexy, for which we may read chronic high blood pressure, Bright's disease, and cerebral hæmorrhage ; and two brothers had phthisis.

She herself had rheumatic fever, which, as I have endeavoured to show, is due to uric acid, and two years later phlebitis in the leg, the relationship of which to gout is well known.

Then the troubles for which she was admitted became worse in the spring, and I have shown that in spring and summer there is a plus excretion of uric acid in the urine, the sign that an excess of it is passing through the circulation on its way to the kidney, while in the winter there is a diminished excretion with some storage of urate in the organs and tissues, the plus excretion of the warm

season being the result of, and to some extent proportional to, the minus excretion of the cold (see fig. 4).

Her attacks were often in the morning—in fact, just at the hours when in the normal physiological cycle the excretion of urate and the amount passing through the blood is greatest, and we have all the signs of its excess in the blood in the cold pale surface and the headaches which so frequently accompanied the attacks, and much the same may be said of the majority of the attacks in the case of Eliza H.

I also wish to refer to Dr. Southey's very interesting case of symmetrical gangrene, which I was fortunate enough to see, and which is recorded in the *Transactions of the Pathological Society*, 1883, p. 286.

The patient was a girl under three years of age. It is recorded that her face and the rest of her skin presented an ashen pallor—"axilla temperature 99·4° F., pulse 120, small and a little wiry at the wrist." (She was evidently passing into the stage of reaction with rise of temperature.) Her urine was alkaline, deposited urates and phosphates, and contained albumin. There could, I think, be no doubt that this alkaline urine contained an excess of uric acid relative to urea, and that the albumin was probably due to blood changes similar to those that produce hæmoglobinuria.

At the *post mortem*, which is interesting as adding one more to the rather scanty records of such observations (Raynaud records only three), nothing abnormal was found in the vessels of the asphyxiated parts, but the blood was everywhere fluid and "like black cherry juice."

In the discoloured parts the skin and connective tissues were chiefly affected, the muscles were only a little stained, and there was no effusion into the joints; and this is interesting, as Raynaud remarks that the lesions are more superficial than one might at first sight expect.

From the parents it was made out that there was undoubted syphilis in the father's family, and he had suffered from hæmatemesis.

The child had an attack of "febrile purpura" in October, and a feverish attack for three days from November 13 to 16.

Her last illness began on the evening of December 1 with headache. Next morning she was apparently well, but at 4.30 p.m. complained of her legs, and her father seeing bruises on them, rubbed them, which appeared to make the pain much worse, and from that time the trouble increased up to her death.

Possibly the final attack was a post-febrile rebound coming after and due to the fever of November 13 to 16, similar to the post-febrile condition we see every day after pneumonia, typhoid, scarlet and other fevers, with its symptoms of slow, high tension pulse (post-febrile bradycardia), subnormal temperature and general depression, which are due to the urate, which is stored during the fever, passing through the blood, when, with falling temperature and falling acidity, the conditions become favourable to its solution and excretion; in a word, there is post-febrile collæmia and its symptoms, and Raynaud's disease is, I believe, a mere exaggeration of some of these.

In the case of my patient, Margaret C., the attack bore precisely the same relation to a previous fever, probably scarlet fever.

It may be objected that in Dr. Southey's patient the interval from November 16 to December 1 was too long to allow of this explanation, but possibly the fever did not really come to an end quite as soon as the parents made out, and the way in which serious diseases are allowed to pass almost unnoticed among the children of the poor is familiar to us all. The first sign of this post-febrile collæmia was the headache of December 1; this was followed by a little febrile movement which temporarily raised the acidity and made her appear bright and well next morning, but by the afternoon this had come to an end, and at 4.30 p.m., which comes in what I have spoken of as the afternoon alkaline tide, the full force of the uric acid storm, no doubt reinforced by the temporary fluctuation of the previous night, affected her vessels, and the gangrene began.

A glance at the plate which accompanies the description of Dr. Southey's case shows that the asphyxia affected first and chiefly those parts of the legs which in children of this age are commonly left without covering, and so are exposed to great loss of heat by radiation and conduction; so that Raynaud's argument (given above) with regard to the hands and feet will hold also in this case, for it was the skin and not the deeper tissues that were affected (see previous remarks).

This also has an important bearing on the theory of mechanical obstruction of vessels by colloid uric acid; for if in the blood stream just as in the test tube the precipitation of colloid increases as the temperature diminishes, one would expect to find the worst effects of such mechanical obstruction on the surfaces and extremities of limbs rather than in the deeper and warmer tissues of their more bulky parts.

The most interesting part of Raynaud's thesis is that in which he discusses the etiology of the trouble. He devotes a good deal of attention to arteritis, but sums up against it on the grounds that there is no anatomical proof of its presence, and that permanent changes in the vessels will not account for alterations in circulation which are paroxysmal and temporary. This fact that Raynaud's disease is paroxysmal and temporary, just like the headache, epilepsy or mental depression of which we have spoken, is of itself almost sufficient to suggest that it has a common origin with these other troubles.

The same conclusion is arrived at with regard to the nervous system, though he is himself more in favour of this explanation; but he points out that though a lesion of nerve structure undoubtedly influences the nutrition and sensation of the parts supplied by the injured nerve, the effect is local, and does not affect especially the circulation, while the condition he is describing affects primarily the circulation, the altered nutrition being secondary, and the condition is not entirely local, as the whole surface of the body is affected to some extent in the same way; he finally concludes that spasmodic contraction of capillary vessels gives the best explanation, for the following reasons: The circulation in the arteries is little if at all affected in the paroxysms; the large veins are also free, and obstruction of a vein gives rise to totally different conditions from those met with in the cases he is describing. The chief point in local asphyxia is the extreme slowness with which the venous capillaries refill when emptied by pressure. In an asphyxiated finger, if the capillaries be emptied by pressure, as much as thirty seconds may elapse before they regain their colour; in a normal finger the blood will return in one or two seconds. If a ligature is passed round a finger so as to obstruct the veins, it becomes purple and congested, it is true; but if a pale spot is produced by pressure the blood returns into its vessels even more quickly than in the normal condition. It is evident, therefore, that the obstruction is neither in the arteries nor in the veins, but in the small vessels that lie between them, and the obstruction is spasmodic because, as in the well-known phenomenon of "dead finger," it may pass away and leave no effect behind it. If, on the other hand, the spasm persists for some time, nutritional changes, which, however, are entirely secondary, will ensue. With regard to spasm, it seems at least doubtful whether the capillaries have any muscles that will produce such an effect, and in so far as it is paroxysmal it is now easy to see that it is so for exactly the same reason that headache, epilepsy, and mental

depression are paroxysmal, in accordance with the fluctuations in the causative collæmia.

There is nothing in Raynaud's argument, here quoted, against the possibility that the obstruction is mechanical; on the contrary, it is difficult to believe that spasm of any living tissue can continue so long as to cause its own death. And we can demonstrate that the rate at which the blood returns into capillaries emptied by pressure (capillary reflux) is a reliable index of the quantity of uric acid circulating in the blood, and this can be so only because the obstruction is mechanical and uric acid its cause.

Such being the etiology of the local asphyxia, let us glance at its relationship to other diseases as depicted by Raynaud.

He mentions (p. 72) a case in which the blood was examined, and showed diminution of red cells and increase of white cells, and remarks that this led M. Simon to class the case under the head of leucocythæmia.

Raynaud, however, questions whether leucocythæmia is a disease at all (p. 74), but suggests rather that it is but one symptom of a blood change which has as its results, on the one hand, local asphyxia, and on the other diminition of red cells, increase of white cells, and hypertrophy of the spleen and glands.

This is a view which recommends itself very strongly to my mind; indeed, I had already (*Lancet*, 1892, vol. i., p. 663, and elsewhere) given a similar explanation of the facts before I was aware of this passage in Raynaud's thesis. I have pointed out that in (Eliza H.) an examination of the blood during some of her attacks accompanied by hæmoglobinuria, which was made by my colleague, Dr. S. W. Wheaton, showed increase of white cells, diminution of red cells, and increase of coagulability; and I shall presently give reasons for believing that these blood changes are results of the presence of an excess of uric acid in the circulation.

Dr. Hunter suggests that the excess of uric acid which I found in the urine in these cases was the result of the blood changes and not the cause of them; but I have given (*Lancet*, previous reference) my reasons for not sharing this opinion, and, as we shall see in the following chapter, it is easy to produce definite and distinct changes in the blood at any time by bringing an excess of uric acid into the circulation, and also that the blood itself, even in physiological conditions, varies from hour to hour with the amount of uric acid granules it contains and the quantity of uric acid passing into the urine; I would refer also to some remarks by Dr. W. G. Smith in the *British Medical Journal*, 1896, vol. i., p. 1328, who points out

that uric acid and xanthin are increased in leucocythæmia, while the normal oxidising power of the body is not seriously affected.

The enlargement of the spleen mentioned by Raynaud is interesting (it was also present in Dr. Southey's case), because I have found that in nearly all conditions where the spleen is enlarged (and indeed, as I have pointed out, many others have observed the same thing) there is an excess of uric acid in the urine and in the blood, and I infer that the excess of uric acid was the result of the conditions which produced the enlargement of the spleen, namely, malarial and other fevers, of which I shall speak presently; so that the enlarged spleen and excess of urates in the blood and urine may be mere modifications of that common condition, post-febrile collæmia, which, again, is not uncommonly a cause of Raynaud's disease or allied conditions; so the observed connection between this disease and leucocythæmia is explained, and the changes both in the fluid tissue and the solid tissue are seen to be results of the changes in circulation, nutrition and metabolism which uric acid produces.

The relationship of Raynaud's disease to menstruation and pregnancy is of considerable interest, though Raynaud only narrates one case in which the symptoms underwent a monthly exacerbation, and even here we are not told, as he remarks, whether the attack coincided with the period. I should, however, have very little doubt that this was so, for I know of no physiological condition in which an excess of uric acid in the urine and blood is more certain to be met with than in menstruation (see figs. 31 and 32).

As a matter of every-day observation, all conditions which upset nutrition and interfere with the taking and absorption of food at once produce a fall in the acidity of the urine and an increased excretion of uric acid; and menstruation, even when normal, and much more so when there is dysmenorrhœa, almost invariably brings about these results; and we get as a consequence of the collæmia so produced the mental depression, headache, fits, and other troubles from which women are so well known to suffer at these times. The same fact explains why women so rarely suffer from gout till after the menopause, because this monthly plus excretion of urates prevents their stores and accumulations of the substance from becoming so large as they do in the case of men.

Raynaud, however, mentions a very good instance of the opposite effects of pregnancy; for just as menstruation lowers nutrition and increases the excretion of urates, so does pregnancy act just like meat diet, sulphate waters and many metals, as a stimulus to

nutrition; up go urea and acidity, and the excretion of urates is diminished—that is, excretion falls below formation, and urates are held back and retained in the body. With this the blood is cleared of urates and the circulation goes on freely. Now Raynaud tells us (p. 48) of a woman who noticed that the complete disappearance of her symptoms was the first indication of commencing pregnancy, and every woman knows that when she is pregnant she is well and strong, unless she has vomiting or some other complication (see remarks about figs 31 and 32).

He says in this case menstruation had no effect on the trouble. Possibly this woman had but very slight menstrual troubles, but the common effects of menstruation on the cerebral circulation and the skin are met with every day, and are too obvious to be passed over.

Here again we can explain a whole series of phenomena; for if pregnancy causes a retention of urates in the body, just as do most fevers and a large number of drugs, such as mercury, opium and others, about which I have written at length; when the pregnancy comes to an end, and urea and acidity fall owing to the interruption of nutrition which parturition occasions, there will be an excessive excretion of urates, the result of the previous retention, and we get what I have spoken of in the case of drugs as a rebound, not post-morphinal or post-febrile collæmia, but post-puerperal collæmia. The cause is in each case the same; the result is also the same. We get obstructed capillaries and the results of this, slow high tension pulse, which may be irregular or intermittent; cold skin and extremities; scanty, it may be albuminous urine; headache; mental depression, and even fits; and, Raynaud (p. 130) mentions two cases of the disease as coming on after recent delivery.

Pregnancy has the same effect on epilepsy (see also interesting case of post-puerperal epilepsy in the *Lancet*, 1894, vol. i, p. 1295), and there is a similar interesting parallel between the effects of pregnancy on Raynaud's disease and on the dangers of chloroform (see p. 397).

See also the most interesting parallel which is presented to us between migraine (the uric acid headache) and Raynaud's disease; for we read in Dr. Liveing's valuable work ("Megrim and Sick Headache," pp. 46, 47), of a woman who inherited the complaint from her father and "became subject after puberty to severe attacks of megrim, recurring at the monthly period, generally immediately after menstruation (see figs. 31 and 32). She married at 20 and had a large family, and it is remarkable

that throughout her pregnancies she had been perfectly free from the complaint, which has invariably returned after delivery."

It will be evident that we can explain every fact here mentioned. Both troubles are due to collæmia, and the effect of menstruation and pregnancy on this is in every case the same. But in one patient the collæmia and the high blood pressure it produced affected especially the intracanial circulation and caused headache. In the other the obstructed capillaries affected chiefly the extremities and produced Raynaud's disease.

Further, we know that the patient who suffered from headache had a strong heart, and consequently when the capillaries were obstructed by uric acid she had high blood pressure, of which the headache was at once the result and sign; while the patient who had Raynaud's disease had a weak heart, so that the obstruction in the capillaries was able to interfere seriously with the circulation in certain portions of the extremities; just as I shall have to suggest in chapter xvi. that the strength or weakness of the heart determines whether the same forces shall produce headache on the one hand or chorea on the other, or, as I have already suggested in chapter viii., whether they produce depression on the one hand or excitement on the other; this association with a weak heart accounting for the great frequency of chorea in girls, and of conditions of excitement in women, just as it here accounts also for the preponderance of girls and women among sufferers from Raynaud's disease, 80 per cent. of Raynaud's cases being, as we have seen, females.

No doubt a series of anatomical and physiological, or even pathological, conditions determined in each case the locality to be most affected; but these are of little consequence because, as I have shown, if the blood is kept moderately clear of urates, neither kind of disturbance would take place, and Raynaud's observation on the circulation in the skin has now given us the power of estimating the uric acid in the blood by a touch with the finger.

With regard to irregular pulse, Raynaud mentions several cases in which this was observed, and he looks upon it as a purely nervous phenomenon. I have pointed out, however, that my pulse never falters or flutters except when I am suffering from obstructed capillaries and high blood pressure, and that this does not appear when my blood is kept free from any great excess of uric acid.

As to fevers, Raynaud mentions (p. 55) the case of a woman who had some attacks of ague in March, and about the middle of April began to be very easily affected by cold, so that exposed portions of her body became pale and then slate-coloured.

In one of my cases the attack came after a fever, and in another it came in a period of extremely low nutrition, perhaps due to insufficient food; and I have suggested that Dr. Southey's case was also due to post-febrile collæmia.

Now fever, as I have just pointed out in the parellel case of pregnancy, increases metabolism; the excretion of urea and of acid rises, the alkalinity of the blood is diminished, and as a result it is cleared of urates, and the excretion of urates in the urine is diminished to a corresponding extent; but the blood being cleared of urates, the capillaries are freed, and we get a quick low tension pulse, and as we now know also a quick capillary reflux. The urates are, however, not merely kept out of the blood; they are also kept out of the urine—that is, are kept back and retained in the body—and when the acidity falls at the end of the fever, out they come again, flooding the blood with an excess of urate, and producing post-febrile collæmia, with all its signs and symptoms, prominent among which are slow high-tension pulse with slow capillary reflux and scanty urine; so that the relaxed pulse of fever and the tense pulse which follows it are the simple results of the altered metabolism through its effects on the quantity of urates in the blood (see p. 200).

Then Raynaud mentions what I regard as most undoubted and independent signs of free and obstructed capillaries without having himself understood their import, for on p. 99, in describing an attack, he tells us that the urine is small in quantity, and on p. 121 he says "Quelquefois chaque accès se termine par une abondante émission d'urines."

Could anything prove more completely that general obstruction of capillaries is present at the time of the attack, and is subsequently removed?

An interesting case of this disease is recorded by Mr. D'Arcy Power in the *Lancet* (1893, vol. ii., p. 249) in a girl, aged 4 years and 8 months, and the patient's mother "volunteered the statement that before the attack the patient passed much more urine than usual." This diuresis no doubt corresponded with the mental well-being which in older patients is frequently noticed to precede headache or fits (see pp. 245 and 264).

Under all conditions, both in physiology and pathology, the excretion of water in the urine is from hour to hour and day to day inversely as the uric acid; and as the urate excretion can be controlled by drugs, the excretion of water can also be controlled.

I have also pointed out that it has been shown that digitalis,

which is well known to contract the arterioles, does by this contraction reduce, or even completely arrest, the flow of urine (see fig. 33), and have suggested that a similar obstruction of the capillaries of the kidneys by uric acid accounts for the inverse relation between water and uric acid in excretion.

In Raynaud's disease, therefore, we have evidence not only that the capillaries are obstructed in the affected part and over the surface generally, but we also have evidence that they are obstructed in the kidneys in the fact recorded by Raynaud that the urine is scanty; and in the fact that the attacks may come to an end with a diuresis we have evidence that the vessels are freed or dilated not only in the affected area and the skin generally, but also in the kidneys.

I would also point to the interesting parallel between the attack of asphyxia on the one hand and the uric acid headache, epilepsy, and hysteria on the other. In all of these the attack is contemporaneous with a scanty secretion of urine, and is followed by more or less diuresis.

But if Raynaud had investigated any of the other secretions, they would have told him the same story, for the saliva is scanty at the same time, and for the same reason, that the urine is scanty; and I see good reason to think that the gastric juice, the bile, and the other secretions are similarly affected. Nor are we without similar evidence in respect of other organs, for in all my three cases, and to some extent also in Dr. Southey's, the headache, mental depression, and bad temper which accompanied the attacks gave plenty of signs that the intracranial circulation was far from satisfactory; and in the case of Eliza H., when drugs appeared to prevent her attacks, one of the most marked concomitant signs was a decided improvement in temper.

The fact is that in collæmia the vessels all over the body are obstructed, and all the most important organs and tissues give evidence that their functions are thereby disturbed; and the relation between Raynaud's disease and certain neuroses, such as hysteria, epilepsy, and the headache and mental depression of which I have spoken, amounts simply to this, that they are all effects of collæmia, and for this reason often occur together; and these disturbances, which seemed to Raynaud to show that the nervous system had some hand in the causation of symmetrical gangrene, merely prove that the disturbance of circulation which produces the gangrene in the extremities produces also such changes in the intracranial circulation that certain contemporaneous changes in the functions of the great nerve centres result.

I do not assert that the nerve centres produce no such effects, but, when they do so, these will not be influenced by controlling uric acid, either by drugs or diet, and I only claim those things as due to uric acid which are so influenced.

What these changes will be depends in any given case on a variety of other general and local conditions, in addition to the collæmia common to all, and will vary according as the local conditions favour or counteract the effects of the collæmia on the local circulation.

A most interesting case, in illustration of these remarks, is recorded by Dr. C. Crawford Aitken in the *Lancet*, 1896 (vol. ii., p. 875), where attacks of Raynaud's disease came in association with the phenomena of uræmia.

His patient was a man, aged 43, who had a family history of gout, renal disease and epilepsy, and had himself suffered from chronic Bright's disease for six years. He had also suffered from occasional attacks of Raynaud's disease for seven years.

There were the usual cardio-vascular signs of Bright's disease, and the pulse showed increased tension during the attacks of Raynaud's disease.

The point, however, specially brought out in this paper, and it is a most interesting one, is that in five out of seven attacks of uræmic convulsions there were concurrent or closely related attacks of Raynaud's disease.

Obviously the explanation of this is similarity of causation; the obstruction of vessels which produced Raynaud's disease in some parts of the extremities caused also a rise of blood pressure or cardiac failure sufficient to produce convulsions in the manner explained in previous chapters.

Another point of great interest in Dr. Aitken's paper is the relatively low urea on the days of attacks of Raynaud's disease or convulsions, thus on days of attack the urea ran from 120 to 280 grains, and on free days from 200—320 grains.

I cannot agree with Dr. Aitken that this had anything to do with spasm in the vessels of the kidney, *i.e.*, was due to defective excretion of urea; because it was obviously due to deficient formation of urea from obstruction to the circulation throughout all the tissues of the body, which I have shown does occur with every rise in the excretion of uric acid, even in physiology; and have specially pointed out in chapter viii., with reference to the causation of fatigue.

Dr. Aitken's careful observations of the urea are of the highest

interest, for they prove, if further proof is needed, that uric acid was high in relation to urea on the days of the Raynaud's attacks and of the uræmic fits; and we already know, from the observations of others, that urea is low during all kinds of epileptic and hysterical attacks, and rises as the attack passes off.

No doubt in Dr. Aitken's case the renal vessels were obstructed just as those of the retina which he saw, but so were also those of the liver and muscles, and the low urea was due to defective formation and removal from these.

On the other hand, if the deficient urea is due to defective elimination by the kidney, why is there not also defective elimination of uric acid? But in all these conditions I have shown that there is a large excretion of uric acid.

The answer is simple. There is a large excretion of uric acid because there is excess of it in the blood; but urea is not in excess in the blood, on the contrary it is deficient, as shown by the late Professor Semmola in the case of Bright's disease (see chapter xiii.); and in physiological conditions we can control the excretion of urea along with the phenomena of fatigue by controlling uric acid, showing that the one depends on the other.

In the above interesting case the urine occasionally contained hæmoglobin as well as albumin.

I quite believe that there are people "whose heads have never ached," but it would not at all follow that they had never had collæmia, but rather that the conditions of their intracranial circulation were such that high blood pressure disturbed them but little; in others, again, the local conditions might favour circulatory disturbance by high blood pressure, and these would suffer with headache even in slight collæmia; and the local conditions giving rise to these differences of effect may be anatomical, physiological, or pathological.

Syphilis is mentioned by Raynaud as an antecedent in two cases, and there was a history of congenital syphilis in the father of Dr. Southey's patient; and this, it seems to me, is just one of those things which may so alter local conditions as to render parts previously enjoying immunity liable to the worst effects of collæmia and the high blood pressure which it produces.

Thus syphilis may produce such changes in bone, membranes or intracranial contents as will make all the difference between collæmia and high blood pressure, seriously affecting the intracranial circulation and hardly affecting it at all; and in the extremities syphilis may produce such changes in the vessels as may make the difference

between mere cold hands or "dead finger" and a regular attack of Raynaud's disease, the collæmia being the same in both cases.

It will be evident, then, that in claiming Raynaud's disease as an incident in collæmia, I by no means seek to exclude other factors which may both intensify the action of the collæmia and determine the locality which shall suffer most.

Probably the preponderance of girls and women among the sufferers from Raynaud's disease is due to their having less muscular power and activity than males of the same age: for there can hardly be any doubt that any weakness of the left ventricle would greatly increase the evil effects of obstructed vessels on the nutrition of the extremities, and we shall see further on that it has a similar effect in cases of Bright's disease.

Again, if, as some assert, it was a muscular contraction in the arterioles that caused the obstruction in the circulation, why should women suffer more than men? Why should the woman's heart fail to overcome the obstruction when the man's succeeds?

For if it is a case of muscle against muscle, there is no reason why a woman's heart muscle should not be just as strong in relation to her arteriole muscle as a man's heart muscle is in relation to his; but when we come to the mechanical obstruction produced by particles of uric acid in the circulation in the capillaries, the obstruction to be overcome may be as great in the woman's capillaries as in those of the man, and her weaker heart muscle may fail to overcome it, while the man's stronger muscle may succeed in keeping the circulation going.

Here we have, I think, a further argument against muscular, and in favour of mechanical, obstruction.

Again, if the fits of childhood are more often due to high blood pressure in the intracranial cavity than to heart failure, we can understand why boys, with their better muscular development and stronger hearts, should more often suffer from fits than girls, so that difference of muscle power may suffice to explain the different incidence of these two diseases on the sexes.

Opium was the drug of which Raynaud made most use in treatment, and he raises the question of its action on the muscular fibres of the arterial coats, the relaxation of which is his chief object. He mentions Pott's unbounded confidence in it for the cure of gangrene, but seems to think it is of use chiefly as a narcotic.

I have shown that in conditions of collæmia and high blood pressure opium frees the capillaries and produces diuresis by raising the acidity and clearing the blood of uric acid (see fig. 15);

and this action of opium, causing storage and retention of urates in the body, is followed by a rebound, just as in the parallel cases of fever, pregnancy, and the seasonal variations in excretion mentioned above; and we have, as the action of opium comes to an end and the acidity falls, not a post-puerperal or a post-febrile collæmia, but a post-morphinal collæmia; and I have also shown, with regard to this latter, that if the urate is removed by a few timely doses of a salicylate, the post-morphinal collæmia, with all its signs and symptoms (slow high tension pulse, slow capillary reflux, scanty urine, headache and mental depression) fails to appear. Exactly the same thing applies also to post-plumbic and post-mercurial collæmia.

In a word, it can be shown that every drug which frees the capillaries and lowers blood pressure, producing increased excretion of urea, rise of surface temperature, increased excretion of water from the lungs and kidneys, diminishes at the same time the uric acid in the blood and urine; conversely everything that increases the uric acid in the blood and urine produces the reverse effects; and even mere absence of uric acid from the blood and urine as the result of previous excessive excretion has the same effects on the circulation as the drugs that remove it from the blood. It is impossible, therefore, to admit that the facts prove that any one of these drugs, such as opium, has a direct effect on the contractile tissues of the arterioles or capillaries; their effect is dependent on uric acid; and it is easier to believe that uric acid affects the capillaries mechanically by obstructing them than as an irritant causing spasm and contraction.

I believe that post-febrile collæmia with its results might be prevented by a similar usé of salicylates during the fever (see also chapter xiii. as to their value in scarlet fever).

Here we have a disease which, like those mentioned in previous chapters, is paroxysmal in relation to the more or less natural fluctuations in the excretion of uric acid, and we see that it holds this relation because it is due to the obstruction of capillary vessels which an excess of uric acid in the blood produces.

We have seen that Raynaud's disease affects especially the superficial structures and the extremities, and I need not go into any great detail to suggest that many minor changes in the nutrition of the skin are similarly related to the effects of uric acid on its circulation. If so, we have at once a simple explanation of a large number of points in the cause and cure of skin diseases.

Thus the relation between erythema and urticaria on the one

hand, and acute rheumatism on the other, may be explained by supposing that the skin trouble corresponds with the excess of uric acid in the blood, while the arthritis corresponds with the driving of that same uric acid out of the blood into the joints, thus it is not uncommonly seen that when a patient suffering from psoriasis develops articular gout the skin trouble disappears; and the same with rheumatism, the erythema and the arthritis do not generally originate together (see *Lancet*, 1888, vol. i., p. 523).

Again, if, as we see in fig. 5, uric acid affects the circulation in the skin so much as to alter its temperature from hour to hour in physiological conditions, it is no great step to suppose that it may occasionally affect its function and structure.

Then we all know the relationship between dyspepsia and certain eruptions, or, again, between menstruation and eruptions; and in both these conditions, as I have shown, an excess of uric acid is to be met with in the urine and the blood.

Again, fevers are followed by post-febrile collæmia with slow high tension pulse, mental depression and subnormal temperature, and in this condition, just as we should expect, boils and papular eruptions which are very prone to ulcerate and slow to heal are met with, and I have myself seen quite a number of such cases after typhoid fever and pneumonia.

Alopecia, again, is not a very uncommon post-febrile symptom, as I have seen and read of several cases in the last few years (see *British Medical Journal*, 1890, vol. i., pp. 1027 and 1239); and a case which I saw myself had this very suggestive connection with season, that while the hair had on several occasions grown during the autumn and winter, it had fallen off again in the following spring. After what I have said as to the seasonal variations in collæmia and the excretion of uric acid (fig. 4), I will only point out that this case of alopecia parallels in the most striking manner the uric acid headache, mental depression, suicide, asthma and phthisis, as well as the disease we are specially concerned with in this chapter, and I cannot but think that some community of causation lies at the root of this parallelism.

Again, we can easily understand how such drugs as acids, opium, the iodides, calomel and thyroid gland or extract (Dr. Davies, *Lancet*, 1893, vol. ii., p. 399) act in curing these skin diseases, for all these substances have this point in common: that they clear the blood of uric acid (see chapters iii. and iv.; also *British Medical Journal*, 1888, vol. i., p. 27, and 1892, vol. ii., p. 165; and *Lancet*, 1888, vol. ii., p. 63).

I have for some time been in the habit of treating skin troubles, originating in connection with any of the above-mentioned disturbances of nutrition, with drugs which clear the blood of uric acid, I think with considerable success.

Then if the vessels of the skin are obstructed by uric acid so that surface temperature is reduced and even the nutrition of the skin is affected, it is probable that in those capillary vessels where the circulation is at a standstill the walls of the vessels themselves will suffer in their nutrition and deteriorate, so that when the blood again passes into them they may bulge and leak, and thus small extravasations of blood result.

If this is the explanation of purpura it almost amounts to a demonstration that the action of uric acid on the capillaries is not that of a mere irritant on a living tissue, for it is hardly possible to believe that any tissue could keep up a spasmodic contraction while its substance is actually being disintegrated.

In this way purpura may be connected with uric acid and the changes it produces in the circulation, and this will explain its connection with the rheumatic group and also with chronic Bright's disease, dyspepsia, post-febrile conditions, and menstruation (see *British Medical Journal*, 1890, vol. i., p. 596, and 1901, vol. i., p. 1535; and *Lancet*, 1891, vol. i., p. 658, and 1891, vol. ii., p. 933, and 1902, vol. ii., p. 286; and *British Medical Journal* Epitome, May, 1893, p. 80).

Thus the association between Bright's disease and purpura and other terrible and even fatal skin lesions is easy to understand, for in Bright's disease we meet with the slowest capillary reflux, the most intense collæmia, and the largest number of granules in the blood.

And when we administer an iodide with the object of clearing the blood of uric acid, it is little wonder that we sometimes precipitate this on the skin and produce a more or less severe inflammation. And skin irritation having this causation can be relieved or prevented by solvents, and I now often give salicylates along with iodides to prevent the more severe effects of retention. These very severe skin irritations are often accompanied by a decided rise of temperature, in fact, we have all the signs of acute gout of the skin. We have, then, two classes of skin trouble: (A) Those due to direct irritation—gout of the skin; and (B) those due to the vascular effects of uric acid, which are the effects of collæmia on nutrition. Thus solvents like sodii bicarb. will cure the A group, but may produce a member of the B group in its place. A retentive drug, as an iodide,

will relieve the B group, but may perhaps produce a member of the A group, and the effect of the drugs will tell us in each case which group we have to deal with, if we are otherwise in doubt (see also chapter ix.). The common use of salicylate ointment in eczema and psoriasis points, I think (even if their relation to arthritis did not also point to it), to their being a gout of the skin, that is, a local precipitation of urates in the fibrous tissues of the skin, and hence they belong to Group A (see also pp. 135-136).

I may mention also some experiences with cases of psoriasis; thus a patient of mine, a woman, aged 23, tells me that she has had psoriasis since she was 11 years old. She has had two children and in each case the psoriasis has been better during pregnancy and worse afterwards, and she has now come (July, 1899) because it has been much worse in the six weeks since her last child was born. And the parallel effects of pregnancy in headache, epilepsy and Raynaud's disease will not escape notice, and we already know that menstruation has just the opposite effect. Again, the treatment of psoriasis with salicylates has brought to my notice a point that may prove to be of some interest.

It is, I think, common experience among dermatologists that salicylates relieve or cure psoriasis, but so far as I know they have not noticed that the drug acts differently on covered and uncovered parts.

I first noticed this in a patient I saw in 1898, a girl who wore sleeves only to the elbow and short petticoats, and suffered from general psoriasis. I gave her salicylates as usual, and in a week or two she returned with the arms below the sleeves nearly well, while the upper parts of the arms were nearly as bad as before, similarly the exposed parts of the legs were well, while the upper parts of the thighs were nearly as bad as ever.

I could not help noticing so great a difference, and I could not help noting also the parallel between the action of salicylates in this skin disease and in subacute conditions of gout and rheumatism.

Then the young woman I mentioned with reference to the effects of pregnancy afforded a further instance of the same thing, for when I put her also on salicylates, the weather (July) being, of course, rather hot, I found that in a few weeks the uncovered parts (face and hands, which were the worst of all at first) were nearly well, while the covered parts of the arms and chest were still bad.

I then gave her directions to clothe very lightly and keep as cool as possible, and she got better and ceased to attend.

These, and other cases, of which I have no room to give notes, led me to regard it as probable that salicylates cure psoriasis by removing urates from the skin, and that the solubility and removal of urates is facilitated by cold and hindered or prevented by heat, just as we know is the case with these drugs in subacute gout and rheumatism; in all these diseases, while salicylates are in circulation, cold or exposure to cold makes the local troubles better; where there are no salicylates cold makes them worse.

And this is the reason why this effect of salicylates was most marked in cases of this skin disease that came under my care in the warm months, for then parts even lightly covered might be subject to much heat and perspiration.

If my observations are confirmed by others, and if my reasoning is correct, psoriasis is a gout of the skin, and its relation to collæmia is the same as that of gout or rheumatism to collæmia; the collæmia provides the presence of the urates, which are afterwards precipitated on the joints or the skin tissues.

I may also mention that I have heard from Dr. Edgar J. Spratling, of the Massachusetts Hospital for Epileptics, that he considers "that uric acid is a main factor in urticaria," and he gives references to the *New York Medical Record*, vol. xlvii., No. 22, p. 690, and the *Lancet*, 1895, vol. i., p. 1595, where among other cases he records having noticed an excess of uric acid in the urine and the presence of some uric acid in the blood, in a female, aged 24, suffering from dementia and urticarial wheals.

This is, no doubt, good evidence of the association of urticaria with excess of uric acid in the blood and urine; but it does not help us to decide whether the skin trouble was due to the defective skin circulation of collæmia, which we can now measure by the time of the capillary reflux, or to direct urate irritation, as in gout or rheumatism, which now seems to be a possible explanation of psoriasis.

I may say, in reference to this, that in my experience erythema, and certainly erythema nodosum, is made worse by salicylates, which increase collæmia; while it is made better by a drug such as an iodide, which clears the blood of uric acid and puts an end to collæmia; we must also remember that the erythemata do not tend to occur along with acute rheumatism when the blood is cleared of uric acid, but to alternate with it, that is, to coincide with conditions of collæmia.

It looks, then, as if erythema may prove to be due to the circulation conditions produced in the skin by collæmia, and its wheals may be due to a minor condition of the changes which I have already suggested as the cause of purpura.

And in accordance with this reasoning is the fact that where urticaria is associated with purpura the extravasations begin in the centre of the wheal, just at the very place where the obstruction of capillary circulation has been most lasting and severe, and I have myself had the opportunity of watching a case thus progressing from urticaria to purpura; the extravasations began in the centre of each wheal, so that they at first resembled the familiar skin records of pulex irritans.

Psoriasis, on the other hand, being due to a gout of the skin, is relieved by a salicylate, which makes erythema worse, but gout and rheumatism better.

A patient tells me that he himself and seven of his children all suffered from eczema capitis in childhood, while an eighth child born after he and his wife had gone on to a uric-acid-free diet was the first to escape; and the mere occurrence of eczema in the precipitation period of childhood shows it to be a precipitation disease (see p. 236), and I have records of a number of cases in which either chronic eczema or psoriasis have improved or vanished on a correct diet.

I give these facts for their own intrinsic interest, as a contribution to be tested and proved, or disproved, as the case may be. All that is really certain is the relationship between certain skin troubles and uric acid, and the more closely this relationship is investigated the more important does it appear.

Speaking of pulex irritans reminds me of a fact I can answer for in person, as well as in others, viz., that of late years, since I have got more and more free from collæmia, I have been less and less troubled by that ubiquitous parasite, and when he does attack me, instead of the large raised wheal that used to result, I have only a small flat circular patch of dilated vessels.

Is the wheal of an insect bite but a local collæmia causing stasis and effusion in the interstitial tissues, a collæmia due to some acid injected, and is that stasis and effusion more or less absent when the uric acid for collæmia is no longer available?

It even looks as if the insects know that the stasis and hyperæmia, which they produce, no doubt for their own benefit, are not likely to come off, and so they do not trouble to make any punctures or remain on the individual in question.

My impression is that I have acquired a similar relative immunity against gnats and field-bugs in general, and certainly a few years ago I had to spend many shillings a year on pyrethrum roseum, of which I now never use a grain, while I see no reason to suppose

that my hospital patients are any more free from attacks of pulex irritans than they used to be.

An illustration of these facts comes to hand from Lilla M. Tenney, M.D., of Oakland, California, who in a letter dated June, 1906, writes: "I have been greatly interested in the verification of the statement in your writings of the effect of pulex irritans before and after following a uric-acid-free diet. Fleas are the pests of California, and during my fourteen years residence in the State I have been so tortured by them I have thought they would do what earthquakes could never accomplish—drive me back East to live. For the past six months they have become noticeable for their infrequent attacks, and I rarely have one on me now. It is worth going without meat to obtain this relief alone."

I have reason to believe that those on a completely uric-acid-free diet have a similar relative immunity from mosquito bites, and thus obtain a double protection against malaria (see also chapter xii).

We have seen that Raynaud did not favour the idea that the troubles he described were due to local nerve lesions or neuritis, though it is held by some to be due to disease of trophic nerves or their centres;* but possibly the relation between Raynaud's disease and neuritis is that both may be due to uric acid (see also Dr. Buzzard's opinion in the *Lancet*, 1893, vol. ii., p. 1233). I have myself also heard from Dr. Mackie, of Lowdham, Notts, and others, of cases of neuritis which evidently had important connections with uric acid.

Theoretically one may get a connection between peripheral neuritis and the action of uric acid on the tissues and circulation in two ways, first as a gout of the fibrous tissues in and round a nerve bundle causing pressure, irritation and degeneration, such as occurs, for instance, in sciatica, or possibly also in herpes zoster (and the action of alcohol, arsenic, and several metals in producing these troubles may simply be their effect in driving uric acid out of the blood into the fibrous tissues that support the nerve fibre); second in conditions of collæmia, for as before remarked, stasis and thrombosis have been seen taking place in the vessels of the retina, and it seems but a small step from this to the retinitis of Bright's disease, associated with similar collæmia, stasis, thrombosis, effusion or extravasation.

Then what takes place in the retina may obviously take place

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* See Dr. Sharkey, *British Medical Journal*, 1896, vol. i., p. 456.

in other nerves and portions of the nervous system, and the stasis and thrombosis may be then also followed by atrophy and degeneration sufficient to account for the symptoms of neuritis, perhaps also for those of some spinal troubles, such as infantile paralysis, which so often seems to originate in post-febrile conditions or gastro-intestinal disturbance, with the collæmia that would no doubt accompany them.

Be this as it may, very many of these conditions are associated with a slow capillary reflux and high blood pressure, and in Bright's disease and neuritis from other causes many of the signs and symptoms undoubtedly tend to clear up as the capillary reflux is quickened and the blood pressure reduced by drugs and diet, and here also, just as in periodic mental disease, I should advise that all abnormal circulation conditions should at once have attention (see also remarks on Tabes in chapter viii.).

I can reckon several cases of retinitis among the most successful cases I have ever had, as showing the effects of diet and drugs on these circulation diseases; and in all cases of peripheral neuritis I have had under observation there have been marked signs of collæmia, and treatment of these circulation conditions has produced some improvement.

On the other hand, some cases called neuritis which have been treated unsuccessfully while the rheumatic element has not been considered, have cleared up at once on salicylates in a way that seemed to place them among the A group of diseases.

Some points of interest have been brought out by other writers, especially with regard to the treatment of skin troubles, chilblains, pruritus, &c., by calcium chloride, a drug which undoubtedly clears the blood and urine of uric acid while it is being taken (see Dr. Savill, *Lancet*, 1896, vol. ii., p. 300).

I have also had a letter from Dr. H. S. Purdon, of Belfast, pointing out that he has long been in the habit of reducing animal food in psoriasis with great benefit, and quoting a paper read at the Dermatological Congress of London, by Dr. Bulkley, of New York, advising this treatment.

The only indication for the treatment of Raynaud's disease and conditions that resemble it is to clear the blood of uric acid as quickly and as completely as possible: they belong to the collæmic group and will be relieved by precipitants; if you cause gout anywhere you will have cured the Raynaud's disease.

For this purpose mercury or its iodide, opium, the nitrites, or ammonium, are likely to be the most useful drugs, and as regards

diet, it will be as well not to administer any uric acid that can be left out without injury to nutrition, and so to avoid such things as soup, beef-tea, meat extracts, tea or coffee, and we must bear in mind that milk diet lowers blood pressure by keeping the blood clear of uric acid, which is what we want to do in Raynaud's disease. With regard to skin diseases the same drugs are of use, and salicylates are also sometimes of great value, and calcium chloride and iodide of potassium are drugs which act in the same way, and are mentioned in some of the experiences quoted above; but diet alone goes to the root of the matter by eliminating and keeping out the cause.

Where acute conditions of Raynaud's disease require prompt treatment, that for acute Bright's disease should be used (see chapter xiii.), and drugs which lower the blood pressure and quicken the capillary reflux should be pushed at first, and afterwards continued in smaller doses to keep up the effect over weeks and months.

As soon as the drugs begin to act and improve the circulation the diet should be altered to one free from uric acid, which should ever afterwards be continued; but it is well not to make both changes at once, and to give the drugs a start of the diet.

When the drugs have got hold and are doing good it will be easier to alter diet, but if diet is altered early and chances to upset appetite or digestion, then nothing will act, and increased collæmia and temporary failure may result.

For the same reason diet changes should be made slowly and with care in cases where the patient does not take kindly to the new foods.

CHAPTER XII.

Paroxysmal Hæmoglobinuria and Anæmia.

It was the clinical observation of cases of paroxysmal hæmoglobinuria and certain special forms of anæmia that first suggested to my mind the possibility that these troubles, as well as ordinary anæmia, might be due to the presence of excess of uric acid in the blood.

I shall first of all, therefore, mention some of these cases and the results I obtained by investigating them.

December, 1888.—John N. McL., age 4 years and 10 months, said to be subject to attacks of cold and shivering in which he passes red water.

Is generally extra well for some days before the attack, but his bowels are constipated (extra well means retention of uric acid: note the parallel here of what occurs in the headache and epilepsy of uric acid).

Just before the attack he yawns a great deal (sign of collæmia).

His water on the day after the attack is quite clear again.

December 10.—His mother brought him to my out-patient room to-day, saying that he has an attack coming on. Has been taking cod-liver oil and steel wine for the last week. Was this a rebound from the iron, again the exact parallel of migraine?

He is pale and his hands and forearms are cold. Seems dull and heavy, shivering (?). Pulse slow.

I told his mother to sit in front of the fire with him; and in half an hour, at 3 p.m., she came back with the child, and brought some reddish urine he had passed. His face was flushed, and he seemed dull and heavy and said he had a headache; pulse now quicker. His mother says his bowels have not been open for two days. He does not get these attacks unless he is exposed to cold in some way. Have we here a condition in which cold, acting with other causes,

just as in Raynaud's disease, precipitates or greatly increases collæmia? (see fig. 40).

The specimen of urine was reddish-brown, clear, 1024, showed the spectrum of oxy-hæmoglobin, and also that of acid hæmatin, the latter being removed by addition of ammonia. Under the microscope numerous pigment granules, some epithelium, fairly numerous shadowy blood-cells, also numerous granule and pigment speckled casts. No oxalates. Urine, after boiling and filtering, gave urea 1·5 per cent. and uric acid ·06048 per cent. Uric acid to urea 1—15. There was therefore an excessive excretion of uric acid, and probably as the child did not pass water before the attack began, this was a mixture of the urine in the bladder before the attack with that excreted during the attack, or the uric acid would have been higher still.

With regard to this case, I have very little doubt that it was a uric acid storm. He was extra well for a day or two before the attack, just as in uric acid headache and epilepsy (retention), and he was taking a drug which would cause such retention. The attack itself comes at a time—3 p.m.—when there is normally a plus excretion of uric acid (second, or afternoon alkaline tide, see fig. 1), and this collæmia is increased, perhaps as the result of exposure to cold on a December day; all the signs and symptoms of the attack are those of collæmia; and lastly, in the blood-stained urine itself we find excess of uric acid.

For comparison with this I will now give a few notes of the case of a member of our profession, who consulted me on account of uric acid headache.

May, 1888, G. F. T., age 33.—In practice in a Midland county; works hard, lives plainly, fair amount of exercise and riding, occasional hunting. Father has slight attacks of gout, mother rheumatic, and two years ago had peliosis rheumatica.

Previous health.—Slight rheumatic fever nine years ago; occasional joint pains since that; four and a half years ago had rigors and dyspnœa, and was ill three months. Has always suffered from headache, but worse the last four years, sometimes now one every week. He has the pain on waking in the morning, and it remains the whole day. Taking wine at dinner always gives a headache next morning (see fig. 39). His pulse, as observed by his assistant, is slow and of high tension during the headache. He suffers also from depression and irritability, and has cold extremities and rigors during headaches.

Here there is a strong family history—gout on one side and

rheumatism on the other, and every sign of excess of uric acid in his blood or joints. And now we come to the part that bears upon our subject. Also occasionally when he gets cold he has a rigor and a temperature of 102° F., sometimes with joint pains, and passes smoky urine. In the autumn of this year he had such an attack after being out hunting and getting cold, and he kindly sent me some of the urine; unfortunately I was only able to examine it forty-eight hours after it was passed. It was acid, contained a slight excess of uric acid, fairly numerous blood-cells and some oxalate crystals, and gave the oxy-hæmoglobin spectrum. He himself considered that these were attacks of paroxysmal hæmoglobinuria, but the urine was not fresh, and I think that the oxalates were formed out of uric acid and diminished its apparent quantity.

Compare also a short note of a case that came to Sir T. L. Brunton's out-patients' room at St. Bartholomew's, which he kindly allowed me to examine. April 25, 1890, Edward W., age 35.—The case was diagnosed as paroxysmal hæmoglobinuria, and I was given a small specimen of the urine and took a tracing of his pulse; its rate was 112, and yet, in spite of this, the tracing showed considerable tension, as the predicrotic wave was fairly well marked in the down stroke, the predicrotic notch was a considerable distance above the base line, and the dicrotic wave only of moderate size. The second sound of the heart was markedly loud. We were here probably just at the end of the cold stage and the beginning of the fever.

The urine was like pure blood, but showed no blood discs under the microscope, and after removal of albumin it yielded urea 1·4 per cent., uric acid ·12768 per cent.; relation 1—11—an enormous excess of uric acid and a relation to urea never met with in health.

Dr. L. G. Guthrie has an interesting paper on "Idiopathic or Congenital Hereditary and Family Hæmaturia," *Lancet*, 1902, vol. i., p. 1243. In this he refers to some cases previously published by Dr. W. H. W. Attlee, one of which was under my care at the Metropolitan Hospital. I may say that in the case under my care there were distinct vascular changes at the time of the attack, the capillary reflux was slow and the blood pressure high relatively to the age and weight of the child, and I regarded the fits as corresponding to the headache, dulness, or sleepiness met with in other cases; while the rise of temperature, followed by hæmaturia, had an identical causation with that in other cases

recorded in this and the previous chapter, and even the congenital or hereditary history need not, I think, greatly surprise those who know how strongly hereditary is the common uric acid storm (migraine) with which these cases present to my mind such an obvious parallelism.

I did my best to put the child that I saw on a uric-acid-free diet, but the mother, I fear, either would not or could not do what was wanted, and the child will thus lose its best chance of avoiding its father's fate. That the father died of uræmia shows how these cases, as I have pointed out, eventually end in Bright's disease, of which, as we shall see in this and the next chapter, their causation is an epitome.

Dr. Guthrie calls these cases "mysterious," but I see no mystery. The pathology of migraine is simple and well known, and from migraine with its paroxysmal albuminuria to epilepsy, with paroxysmal hæmaturia, seems to me but a simple progression from bad to worse; and even in the same individual we may have one attack producing migraine, another epilepsy, and after one attack of either there may be now albuminuria only, now hæmaturia as well.

I will also mention a case which, more than any other, opened my eyes to the probability of uric acid producing destruction of red cells and so anæmia.

July, 1889, a lady, aged 46.—A patient under the care of Sir T. L. Brunton, during whose absence from home I saw her. Had a gouty family history, but never had gout herself.

She complained that she had "anæmic attacks" which she was sure were connected with gout. She had lived a healthy outdoor life, and often played cricket with her children, now growing up.

Her face was tanned by exposure to the sun; but through this and also in tongue and gums there was every sign of intense anæmia; I felt sure that she must have had a hæmorrhage, and suggested loss of blood by piles—which she had to a slight extent—or by excessive menstruation; these, however, she denied, and maintained that she had suffered off and on from this anæmia, which came in attacks, and was in some way connected with gout. So far as I could make out from her description, the attack after which the anæmia appeared was of the nature of a bilious attack or sick headache, but she had no hæmaturia. Have we here hæmoglobinæmia not sufficient to cause hæmoglobinuria, but lasting longer and producing the intense anæmia I saw?

This raised in my mind the question, is collæmia a cause of more

or less destruction of red cells, and does it in this way bring about chronic and recurring anæmia? And having once been led to regard anæmia from this point of view, I was not long in coming on other signs of the possible production of anæmia by uric acid. I have also pointed out in my previous writings that the injection of creatinin into the blood had been shown to produce destruction of red cells (*Comptes rendus de la Soc. de Biologie*, 1877).

August 12, 1890, Daniel H., age 10.—Admitted under my care in the Metropolitan Hospital. Complains of pallor, sleepiness and pains in the head. Father and mother well, five brothers and sisters well. Jaundice as an infant; measles also as an infant. Had a pain in his head on August 1, and a pain in his right side on August 7. Pallor increasing but much worse the last two weeks.

Is now poorly nourished and pale, even bloodless. The conjunctivæ have a slight lemon tinge. Appears intelligent, but dull and depressed. Pulse 120. Temperature 100° F. There is a systolic murmur over the cardiac area. The spleen is enlarged, the notch being at or below the umbilicus, and the lower edge is level with the anterior superior spine of the ileum. Blood shows increase of white and diminution of red cells. He was given liq. arsenicalis ♏ iii., to be gradually increased. During my absence for a holiday he came under the care of Dr. Rolleston, who increased the arsenic to ♏ viii., and eventually to ♏ xii., and added a little digitalis, and on September 17, pil. ferri carb., gr. v., was given twice a day.

On my return in September the child was worse than when admitted, he was not only very pale, but weak and hardly able to sit up in bed. I got a specimen of twenty-four hours urine and found a great excess of uric acid, 1—13·8, and this suggested that his dulness and general misery were due to collæmia, which he had to a very serious extent, even if the severe anæmia was not due to it.

On September 26, the note of the house physician, Dr. Stanley, was: "Still has some pain; extremely anæmic; spleen if anything larger. Hands always tremulous. Pulse 126."

September 30.—I found him in the same condition, lying weak and dull in bed. I accordingly stopped all the previous drugs, and gave a mixture containing ♏x. of dilute nitro-hydrochloric acid three times a day before meals, and another mixture containing sodii salicyl., gr. x., sp. am. arom. ♏xv., three times a day after meals, with the object of affecting collæmia.

Blood examined to-day (that is, before treatment) shows 10 red and 1 white cell to a micrometer square, *i.e.*, 1,000,000 red cells, and 100,000 white per cubic millimetre. Blood examined by Dr. Stanley.

October 7.—Dr. Stanley's note is: "Colour much improved, less tremulous." And this was the beginning of a steady and continuous improvement, so marked as to surprise all who saw him.

October 14.—Weight 3 st. 11 lb. Abdomen 25½ in. at umbilicus.

October 20.—Blood much better in appearance, shows 35—40 red cells per square.

October 21.—Bright and cheerful; up and about, and goes out. Has some colour in face now. Weight 3 st. 13¼ lb. Spleen smaller (?).

October 29.—Weight 3 st. 12 lb. 13 oz.

October 31.—Spleen smaller and more to the left; the notch is now one finger's breadth above the umbilicus. Abdomen 24½ in. at umbilicus.

November 12.—Continued improvement, same drugs. Weight 3 st. 13 lb. 2 ozs. Spleen same.

November 14.—Blood 23 red and 1 white cell per square. All medicines suspended.

November 18.—Weight 3 st. 13 lb.

November 26.—Acids and salicylates begun again.

November 29.—Red cells 35 per square. Splenic notch two fingers' breadth above umbilicus.

December 6.—Red cells 29 per square. Pil. ferri carb., gr. v., given twice a day in addition to other drugs.

December 13.—Red cells 45 per square.

December 17.—Weight 3 st. 12 lb. 6 oz. Going on well; seems bright. Abdomen at umbilicus 23 in.; spleen much smaller.

December 20.—Bright and well. Red cells 37 per square.

January 17, 1891.—Same treatment continued. Red cells 38 per square. White cells not in excess, only one or two in the field. Weight 3 st. 13 lb. 10 oz.

After this he continued very well and was allowed to go home.

I am aware that cases of splenic leucocythæmia have improved on various treatments, or have got well in spite of treatment; but the result in this case followed so immediately on the alteration of treatment as to impress all who saw it with the belief that it was not a coincidence merely.

Since this I have seen several cases of severe anæmia in young women which resisted iron given in the ordinary way (generally pil. ferri carb. in increasing doses) for several months, but improved at once on a course of salicylate of soda; and this drug seemed to affect their spirits and general condition, leaving no doubt in my mind that they had been suffering from severe collæmia.

With regard to the way in which the salicylates produced this improvement I shall have something to say when I come to demonstrate my curves; and similar treatment apparently prevented attacks of paroxysmal hæmoglobinuria and Raynaud's disease (see chapter xi.).

Lastly, I was led to notice that in a number of cases of chlorosis or anæmia in young women, more or less dyspepsia, or even a bilious attack, as in the lady above mentioned, occurring especially at the menstrual periods, held an important place in the history of their trouble; and I knew that these gastric disturbances meant a fall in urea formation and excretion, a fall in the acidity of the urine and a corresponding rise in the alkalinity of the blood, so that this fluid became a better solvent of uric acid and its compounds, and at once took them up in solution from all points of deposit in the body (liver, spleen, fibrous tissues and joints). In a word, the dyspepsia produced collæmia, and it seemed probable that the collæmia produced the blood destruction and anæmia.

Then, in the case of Raynaud's disease with paroxysmal hæmoglobinuria, the notes of which are given in the previous chapter, my colleague, Dr. S. W. Wheaton, kindly examined the blood, and found on several occasions, corresponding with the hæmoglobinuric attacks, a diminution of red cells, an increase of white cells, and an increase of coagulability.

Dr. Wheaton has also given (*Transactions of the Pathological Society*, vol. xlvi., p. 168) an interesting account of the pathology of the black-water fever of West Africa, which appears, as he shows, to have many points of resemblance with paroxysmal hæmoglobinuria. I have little doubt that it represents the effect of severe malarial fever on the excretion of uric acid, and so indirectly on the blood (see p. 200), and it is interesting to note that malarial fever is known to be a cause of "lithæmia" (see my paper in *Brain*, 1891, p. 73) and of Raynaud's disease.

For a case where hæmoglobinuria accompanied an ordinary attack of benign intermittent fever see *British Medical Journal*, 1896, vol. i., p. 590. Yet Dr. Manson seems to think that hæmoglobinuric fever is caused by a different parasite.

The medical journals have contained many interesting records of paroxysmal hæmoglobinuria and black-water fever in the last two years; thus in the *Semaine Médicale*, November 30, 1898, is the record of a case of paroxysmal hæmoglobinuria in a woman of 26, in whom by means of the cystoscope the blood-stained urine was seen to be coming equally from both ureters.

In the *Lancet*, 1898, vol. i., p. 780, Mr. Kellett Smith had an interesting note on the subject, and I wrote a letter which appeared in the same journal, p. 959, pointing out some of the facts I shall mention presently, and strongly advising a uric-acid-free diet and the use of salicylates in malaria to prevent its more serious complications and sequelæ.

Then in the *British Medical Journal*, 1898, vol. ii., p. 866, is a very interesting paper by Dr. Sambon, in which he concludes that black-water fever is very closely related to the paroxysmal hæmoglobinuria of temperate regions, and mentions Dr. Wheaton's facts as to the identity of their morbid anatomy; but he considers that nothing is really known as to the pathogenesis of paroxysmal hæmoglobinuria, and then goes on to suggest a parasitic origin for both.

Among those who discussed Dr. Sambon's paper some interesting points are mentioned by Dr. G. Prentice, of Blantyre, with reference to his experience of the results produced by a change of climate from a low warm level to a high colder one, or by a severe wetting and chill; obviously these changes would produce a fluctuation in the excretion of uric acid, and so collæmia and hæmoglobinuria, just as in this country they produce headache and epilepsy with albuminuria.

On December 20, 1898, the late Dr. W. H. Crosse and Dr. W. C. C. Pakes read a paper on a case of black-water fever before the Pathological Society, in which the attack came on while the patient was in England. It began like an ordinary attack of malaria from which he had suffered in Nigeria, and two days later hæmoglobinuria came on before he had been given any quinine.

They consider that hæmoglobinuric fever is a complication of African malaria, being related to it in the same way that hyperpyrexia is to rheumatic fever.

In the *Lancet*, 1898, vol. ii., p. 1470, Dr. Mackie records a case where hæmoglobinuric fever attacked a patient who had previously suffered from it in West Africa, after returning from a cycle ride against a strong wind; the attack began to pass off after fifty hours and patient recovered. The temperature ran from 102° F. to 103° F. with rigors, but except for the history of a previous attack in Africa there was nothing clinical to distinguish this case from that of Eliza H., recorded in the previous chapter; but from the point of view of causation by uric acid it is interesting that the attack followed fatigue, which would, as we know, bring excess of uric acid into the blood.

The late Dr. W. H. Crosse has also a paper on black-water fever in the *Lancet*, 1899, vol. i., pp. 821 and 885. In this he again favours the theory that it is a complication in the course of malaria, though he mentions Koch's theory that it is not malarial at all, but due to the administration of quinine, and in reference to this he mentions the case of a patient who had no quinine and no hæmoglobinuria while in Africa, but developed it after he had arrived in England in bitter weather.

Here I would remark we have just one of the factors (cold) which helps to develop hæmoglobinuria in this country, as in the cases I have recorded above, which have nothing to do with malaria.

Dr. Crosse further says, on p. 887, that the view of Sambon that black-water fever is paroxysmal hæmoglobinuria is sufficiently demolished by the fact that parasites are found in the blood in black-water fever; but I must confess that I am quite unable to comprehend the logic of this remark.

For surely, if in paroxysmal hæmoglobinuria we have a temporary destruction of blood cells produced by excess of uric acid in the general circulation, liver and spleen, aided by the action of cold on the skin, the effect of which is, as we know, to precipitate more uric acid in the blood and increase the collæmia, then the presence of a few malarial parasites in the blood will not suffice to prevent a precisely similar excess of uric acid, a similar collæmia, and a similar action of cold in increasing it, with a precisely similar effect on the circulation and structure of the blood. If all this can occur without parasites in England, what proof is there that it has anything to do with parasites in Africa?

Indeed, in Dr. Crosse's own case previously referred to, the presence of the parasite did not prevent the cold weather of England from increasing the collæmia and helping to produce hæmoglobinuria.

On the following page he suggests that the hæmoglobinuria is due to accumulation of malarial toxins, which may act as chlorate of potash does on the red cells, and that paroxysmal hæmoglobinuria has an origin in syphilis.

It seems to me that uric acid is the malarial toxin, and it is present and can be demonstrated in the blood; and uric acid, as I have for years been pointing out, does, in conjunction with cold, account for paroxysmal hæmoglobinuria, its association with Raynaud's disease, and for all the most common forms of anæmia as well; in the previous chapter I have already dealt with syphilis in relation to Raynaud's disease.

In the *British Medical Journal*, 1899, vol. i., p. 1325, Dr. G. Thin has an interesting paper on "The Parasite of Malaria in the Tissues in a Fatal Case of Black-water Fever."

In this he passes in review the various theories of causation before giving the facts of the special case, and mentions among other things that out of 40 cases published by a recent observer (Dr. Phlen) no fewer than 30 were due to quinine, "the attacks mostly occurring about two or three hours after its administration."

He also points out that in 21 of these cases quinine was given apart from malarial fever without bad results. He concludes that it was the combination of the quinine and the malarial fever that produced the hæmoglobinuria.

After giving details of his case he gives his reasons for believing that there is no essential pathological difference between black-water cases and pernicious malarial cases without black-water, and concludes that there is no evidence that black-water fever is due to a special form of parasite.

All changes are due to a toxin, the virulence of which is, "in some way not yet explained," increased by quinine.

Then in the *Lancet*, 1899, vol. ii., p. 806, in an interesting article from a correspondent on "The Malaria Expedition to West Africa," is mentioned a case of fatal black-water fever in which no parasite was found in the blood, but the patient admitted having taken large doses of quinine shortly before the attack, and mention is made of other evidence tending to confirm Koch's observations on the connection between black-water fever and quinine poisoning.

From all this two facts stand out: (1) The association between malaria, either past or present, and a form of hæmoglobinæmia and hæmoglobinuria; (2) the deadly precipitating action of quinine in the production of the worst effects of this association, especially when quinine is taken during fever.

The other interesting points are the effects of exertion and fatigue, which we know increase collæmia, and of cold, which we know increases the precipitation of uric acid in the blood, which, acting on the extremities, may so greatly increase the collæmia and stasis that the blood begins to break up, causing a local hæmoglobinæmia; all this we have seen in the case of Eliza H., where attacks of local asphyxia were followed by hæmoglobinæmia and hæmoglobinuria; and this is again but an enlarged version of what any one of us may see for ourselves at any hour of the day or night, that our own blood alters its quality in absolute relation day after day and hour after hour to the amount of uric acid that passes through it and the collæmia and circulation effects it produces.

Of the effects of chlorate of potash which have been mentioned above I know nothing practically, but it has been recorded as producing most severe gastro-enteritis with vomiting and diarrhœa, and we must not lose sight of the fact that in certain cases this would precipitate collæmia and its most deadly effects on the blood and tissues.

This brings us to the action of malarial fever, but its effect is no doubt that of all fevers, only, if anything, more so.

Now the effect of every fever is to clear the blood of uric acid and store a certain amount of this in the body, and the amount stored will be proportional to the amount available and to the severity and sharpness of the fever.

Now it seems to be characteristic of malarial fevers that they come with great suddenness and a sharp initial rise of temperature, and coming in hot countries they must often supervene upon a condition in which there is much uric acid in the blood, and as a result we shall have a very marked retention of uric acid, especially in the spleen, which begins to enlarge.

I say this without prejudice to some points I shall mention later, which appear to show that uric acid is itself the cause of the rise of temperature, and that in its absence, or when taking salicylates, the malarial parasite alone is unable to produce fever.

And what are we to say of the rise of temperature in the case of Eliza H., which came in relation to her hæmoglobinuric attacks, but not in constant relation to them, as there was sometimes a temperature without a hæmoglobinuria. Were they also due to uric acid, a gout of the liver or spleen for instance, in which organs or regions there is sometimes pain along with the fever? They were apparently prevented to some extent, along with the Raynaud's attacks, by the administration of salicylates (compare also what I have already said in chapter x. on the causation of abscess of the liver).

We can now see why in the splenic leucocythæmia case above related, the spleen diminished in size as the uric acid was swept out by the solvent salicylate.

I need hardly point out that the effect on the blood will, no doubt, be proportional to the amount of uric acid available for solution on a given day, and that in malarial conditions, and nearly all diseases associated with enlarged spleen, the excretion of uric acid in the urine has long been known to be large.

We now come to the action of quinine, which, Dr. Thin tells us, is as yet unexplained, and here again our first principles show us

several important ways in which it will increase the uric acid in the blood and the resulting collæmia (see fig. 10).

First of all quinine is itself a xanthin, so that of 15 grains of quinine given, probably 3 grains will pass through the blood and be excreted as uric acid; that is to say, quinine increases the available uric acid by introducing it.

Thus quinine increases the uric acid in the blood of all, but in cases of malarial or other forms of splenic enlargement it enormously increases the collæmia and the excretion of uric acid in the urine.

Lastly, quinine in large doses lowers the temperature and may even produce conditions akin to collapse, while (as we have seen in the case of salicylates in chapter ix.) other drugs which bring much uric acid into the blood and cause severe collæmia will similarly produce fall of temperature and collapse.

What we are at present concerned with is that quinine, both directly and indirectly, increases the uric acid in the blood, that it does this specially in malarial and other cases with enlarged spleen, and that in large doses it produces severe collæmia with collapse and fall of temperature.

We can now see why quinine in combination with malarial fever produces such bad results, for the effect of the fever, here as elsewhere, is to cause a fluctuation in the excretion of uric acid; it clears the blood of it, producing a retention, and this will be large in exact proportion to the amount of uric acid available, which in malarial conditions is always great. The fever then forms an accumulation of uric acid in the liver, spleen and elsewhere, and the larger the spleen the greater the possible quantity. Then comes the quinine and in a few hours reverses all this, and allows a terrific avalanche of uric acid to be poured into the blood stream, a quantity which quickly overthrows circulation, metabolism, combustion, and even the structure of the blood itself.

And every factor of capillary circulation and blood pressure here mentioned can be gauged and measured from hour to hour, and, being rightly understood, can be controlled; this I shall have to point out can be easily done in the case of the post-febrile phenomena of ordinary fevers.

Now let us pass for a moment to the capillary circulation in the finger, for instance; what are the factors that will slow that circulation and the capillary reflux?

We know that the reflux is slowed by anything that increases collæmia, and collæmia is increased by anything that increases

(1) the available uric acid and (2) the cold to which the circulating blood is exposed, so that it is a matter of every-day observation that a capillary reflux of five is slowed to six by cold or quickened to four by heat.

The reflux is also slowed by anything that diminishes the *vis a tergo*, that is, the power of the heart; hence collapse makes the capillary circulation worse and increases the damage to the blood.

But cold with collæmia in an exposed extremity produces Raynaud's disease and hæmoglobinæmia, which is presently followed by hæmoglobinuria, facts which have been known for a long time.

In chlorate of potash poisoning we have exactly the same factors—intense collæmia with heart failure, collapse, coldness of surface and of extremities. What is here and in all gastro-intestinal irritation the cause of the heart failure? Measure the capillary reflux and you find it slow; measure the blood pressure and you find it high—the collapse is a heart failure and circulation failure before obstruction, part of which at least is due to and proportional to collæmia, and this may be severe enough to cause hæmoglobinæmia.

This is the cause of the collapse so often seen as the result of diarrhœa in children and the similar algide condition of cholera; and this is why the nitrites, which lower the blood pressure and free the capillary circulation, are useful in this condition. The condition is not one of collapse from primary weakness of the heart, but of failure of a normal heart before abnormal obstruction in the circulation, and measurement of the blood pressure and observation of the capillary reflux will serve to distinguish the one condition from the other.

But quinine controls every factor here mentioned, and we can now see why and how it may produce hæmoglobinæmia and may specially do this in bodies that have for months and years previously been under the influence of malaria, and where also there has just been a retention by fever.

I have for many years past been telling all, who were likely to have the opportunity, to use salicylates in malarial fever, and a uric-acid-free diet as a prophylactic; for whatever the exact causation of the fever itself, uric acid obviously plays so important a part in its complications and sequelæ that in the way of treatment at least this much is most strongly indicated.

Indeed, if we were all free from excess of uric acid, we might, as I have said in chapter ix., not only escape the serious sequelæ of

many fevers, such as the rheumatism and Bright's disease of scarlet fever, the rheumatism and thrombosis of enteric fever, the catarrh and morbus cordis of measles, many of which are so clearly associated with the presence of excess of uric acid in the body and blood; but we might even escape the diseases altogether by burning up and destroying the microbes instead of affording them a breeding ground.

And in malaria we have at the time of the fever more or less marked rheumatic symptoms, and later on enlargement and irritation of the liver and spleen, perhaps liver abcesses, the anæmia and hæmoglobinuria, perhaps also leucocythæmia, Bright's disease, gout, gravel, and calculus that follow in some cases I have myself seen (as to Bright's disease of malaria see also Thayer, *American Journal of Medical Science*, December, 1898).

Those who take salicylates with each attack of fever will greatly diminish the frequency and severity of these sequelæ, while those who had lived for years on a uric-acid-free diet might altogether escape them, even if they did not also more or less completely escape from the fever itself.

Uric acid may not be the only cause of these troubles, but when it has been removed we shall see what is left, and so far results have been very good.

It may be said that the vegetarian natives of India ought to be free from fever, which we know is not the case; but unfortunately for themselves they take pulses, which, as we shall see in chapter xvii., contain more, sometimes twice as much, uric acid as meat itself; these natives have no freedom from uric acid, and their suffering is therefore no proof that those who live on a really uric-acid-free diet might scarcely suffer at all.

The cases of which I give notes might raise the question whether the attack of malaria would occur at all if the body were free from excess of uric acid. I should be sorry to found any conclusion on a few cases. I give them rather to encourage others to pursue a line of treatment which I have been advocating for some time past, and which, if it does no good, can probably not do harm; and the good effects of salicylates in malaria have been matter of common knowledge for some time, though just as in acute rheumatism and scarlet fever no adequate explanation of their action has been forthcoming, except their influence on uric acid (as to scarlet fever, see observation of Professor von Jaksch, mentioned in chapter xiii.).

T. C., aged 37, a native of Africa resident in England for purposes of special study. Has suffered from malaria and also had

some dysenteric trouble and abcesses in the liver, one of which was operated on. He had rheumatic fever in 1892 (a result of fever and accumulation of urates, I remark).

He came to me in the early part of 1899, complaining of febrile attacks coming every second week for six months, and recently after a bad cold still more frequently.

He is pale, blood decimal ·3, thin and losing weight. His pulse is 84, capillary reflux slow, blood pressure 140—150, and the second sound of the heart is loud.

On the abdomen is a scar above and to the right of the umbilicus to which the liver is fixed, the lower border being about the level of the umbilicus, while the liver dulness is diminished above, so the liver is pulled down rather than enlarged.

The spleen cannot be felt and there is no increase of dulness in that region. The bowels act once a day, the urine is free from albumin and sugar.

I proceeded to put in force the treatment I had advised others to adopt. I gave him salicylate of soda to take during the next febrile attack, and told him to alter his diet to one free from uric acid, with a liberal allowance of fruit.

Two weeks later he reported that the febrile attack had come as usual as to time, but was somewhat less severe. He took the salicylate, but it upset him a little at first, but was able to take it better towards the end of the attack.

I advised him to continue the diet and gave him a little nux vomica to be taken with the salicylate in the next attack, to prevent depression.

A month later he reported a great improvement; he had had one threatening of an attack two weeks after the last note; he took the salicylate and it passed off without any actual rise of temperature, and there had been no temperature since.

He only took the salicylate for two or three days, and no drugs at all for the past two weeks. He has improved in other ways, also feels much better in himself, has gained weight on the diet, and his blood is distinctly better. Blood decimal ·45. Pulse 80. Blood pressure 130. I advised him to continue the diet carefully, and to take no drugs unless the attacks threaten to return.

He had previously been having constant febrile attacks, in spite of vigorous treatment by quinine and other drugs. Later in 1899 he began to take meat again as he had no fever, and in the spring of 1900 the fever returned, only to yield once more to the treatment by salicylate and correct diet. This time I hope he will continue the diet.

A similar record comes to hand from a patient who writes from the Punjab, India, in 1901, on which date he had been on my diet for a year: he says, "Previous to commencing the diet I had very bad fevers, with temperature up to 106·5° F. and varying from that to 103° F. for five days at a time, so that for months it was a matter of seven days in bed, ten days well, and then seven days in bed. Although I have not taken a day's leave during the last year (I ride 30 miles a day, with an average of 15 per day in the month), on strict uric-acid-free diet of 2½ or 3 meals per day, I have not had a day's fever or illness of any kind." Did space permit, I could now record several similar cases, and the diet which effects these results does good in all directions, harm in none. Then interesting records of similar points are constantly appearing in the journals. Thus in the *Lancet*, 1901, vol. i., p. 785, Mr. Plimmer speaks of "natural immunity" where patients do not get fever, even though bitten by anopheles "full of the malaria parasite"; of this he says there is not "sufficient explanation." It would be interesting to hear what was, and had been, the diet in these cases, and though it is scarcely possible to be constantly surrounded by mosquto nets, everyone can live on the natural diet.

In these cases of mine it is clear that the parasite (if parasite there was) paid no attention to anything except the diet of the patient, and we have already seen that the parasites of catarrh, influenza and pneumonia may have a similar respect for it.

My experience of malaria is, of course, very limited, but I note with interest that Colonel M. D. O'Connell related in the *Lancet*, 1902, vol. ii., p. 662, that he saw in the North-east district of India, a large number of cases of ague in which no parasites could be found.

There thus seems to be a considerable accumulation of facts tending to show that, in paroxysmal hæmoglobinuria, splenic leucocythæmia, chlorosis and anæmia, there is at the time of the blood deterioration a considerable excess of uric acid, both in the urine and in the blood; in the urine I have found it in excess, and in the blood it gives rise to signs and symptoms which are practically identical with those of the uric acid headache (see chapter vi.), and it can now be directly demonstrated in the blood by the Barker-Smith process.

Again, in several of these conditions, a drug (salicylate of soda) which eliminates uric acid and prevents its being present in excess in the blood, appears to produce more or less marked improvement, even when iron or arsenic have failed, while dyspepsia, which brings excess of uric acid through the blood, does harm.

At this point in my investigation the writings of Horbaczeuski and a lecture by Professor A. E. Wright were published, and I therefore said in a letter to the *Lancet*, 1892, vol. i., p. 663, that it appeared to me that these investigators were really mistaking a cause for an effect; and I gave my reasons for thinking that the excess of uric acid noticed in the blood and urine at the time of certain blood changes was the cause of these, and could not be their effect.

I said further that in the case of paroxysmal hæmoglobinuria, it could be proved that the excess of uric acid in the blood and urine at the time of attack was not the result of the blood changes, because it was the result of a fluctuation in urate excretion (minus excretion or retention), which began hours before the blood changes.

In this respect also the excess of uric acid in paroxysmal hæmoglobinuria has an identical causation with the excess in the paroxysmal headache, the paroxysmal fits, and the periodical mental depression described in previous chapters; and in all these alike the fluctuation in the excretion of uric acid is the cause of the symptoms, not their result, or diet would be no use.

At the time my paper on a case of Raynaud's disease was read before the Medical Society (see *Transactions*, vol. xv., p. 156), Dr. Hunter, whose investigations on the blood are well known, said: "In a number of the diseases of the blood of a destructive nature, such as leucocythæmia and pernicious anæmia, the uric acid was greatly increased; there was evidently a direct connection between the two, and he felt sure that the appearance of the uric acid was a result, and was not to be regarded as standing in a causal relation to these diseases." I am glad to see that Dr. Hunter is at one with me as to the facts, and considers that there is a direct connection between them; but I hope presently to demonstrate that the connection is just the reverse of the one he suggests.

All these facts seem to render it probable that uric acid was the cause of the blood changes both in paroxysmal hæmoglobinuria and anæmia.

But I have complete power over the excretion of uric acid in the urine, and if anyone will chalk out a curve on the wall which he wishes his urate excretions to follow from day to day, I will undertake to make it follow a similar curve, provided he follows my instructions as to diet and drugs that effect the solubility of the substance.

It follows that I have complete power over the amount that can pass through the blood, and if uric acid causes the above-men-

tioned blood changes I ought to be able to produce, if not an actual attack of paroxysmal hæmoglobinuria, at least such blood changes as occur in anæmia.

But we have seen in chapter iii. that uric acid taken pure by the mouth passes into the blood (which was to some extent known before) and will in due time pass out in the urine in quantity roughly proportional to that swallowed.

The essential condition of this absorption and excretion of uric acid is that the blood be kept in such state as favours, or at least does not hinder, the solubility of urates; and this can be fulfilled by so ordering the diet as to prevent the alkalinity of the blood being diminished.

It is thus possible to increase the uric acid passing through the blood by the simple process of administering it (grains 1—2 ter) by the mouth; leaving diet and other factors unchanged.

But those who have from diet and other causes but a slightly alkaline blood must not expect to increase the uric acid it contains by taking it by the mouth, for though it gets into the blood of the portal circulation, it is there at once caught up and retained in the liver, and does not pass beyond this till the conditions are very favourable for its solution, both in the liver and the general circulation; and these favourable conditions are only occasionally met with in those who are constantly taking acids, such as beer and wine, or consume a large amount of albuminous food, which, as we know, increases the formation of urea and of acids. And it is a question, in my mind, whether at least some part of the congestion of the liver which beers and wines are credited with producing may not really be due to the irritation produced by the uric acid which they thus retain in it; the acids or acid resins with which spirits are so often mixed having, perhaps, as regards the retention of uric acid, quite as much effect as the alcohol itself. And we now know that the diuretic effect of such wines and spirits is directly proportional to the retention of uric acid they produce.

And in no one (unless the blood is very alkaline) will there be much excess of uric acid in the blood and urine on the day a dose of uric acid is taken, because uric acid itself diminishes the alkalinity of the blood, and interferes for a time with its own solubility *; but on the second or third day after a dose, when the

* This fact I have demonstrated by experiment on animals, the effect of urate injections into the circulation being to diminish the uric acid found after death in the blood.

alkalinity in the blood has again risen, uric acid will begin to be present in excess in the blood, and to pass in excess in the urine, and such excess will correspond more or less in extent and duration to the dose taken (see also *Journal of Physiology*, vol. xv., p. 167).

Our problem, then, is this: Many disease processes in which there are important blood changes appear to be contemporaneous

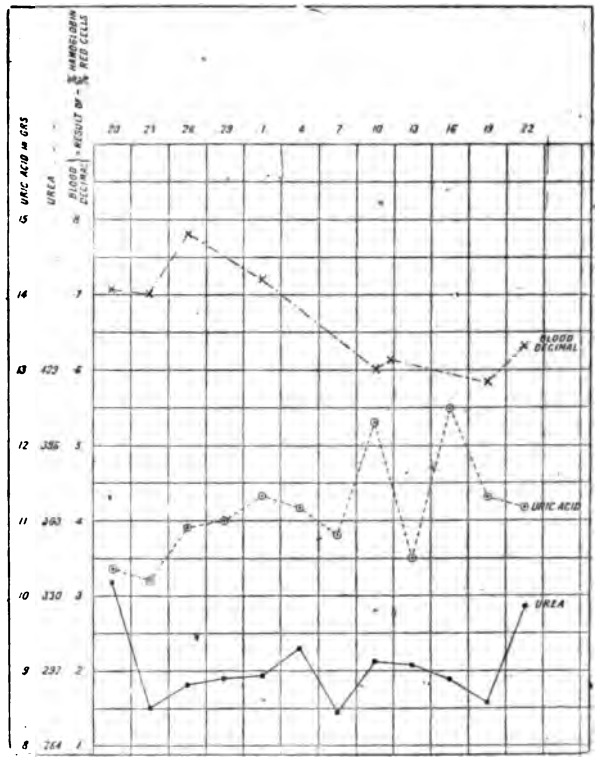

FIG. 50.—CURVES OF URIC ACID EXCRETION AND OF THE BLOOD DECIMAL.

with the presence of an excess of uric acid in the blood and urine, and there are reasons for supposing that the uric acid may be the cause of the blood changes: does the intentional production of an excess of uric acid in the blood bring about any similar blood changes?

On this point I shall allow my curves to speak for themselves with such small explanation as may be necessary.

Before giving them I will say that I have used for this investigation the hæmoglobinometer and hæmocytometer of Sir W. Gowers, and have followed as closely as possible the directions issued with the instruments.

The blood decimal is the result of the fraction $\frac{\text{per cent. hæmoglobin}}{\text{per cent. red cells}}$, or if $\frac{100}{100} = 1{\cdot}0$, though the results are generally decimals, as in the following curves; and I agree with Dr. A. E. Garrod, Dr. Wilcox and others (*Proceedings of the Royal Medical and Chirurgical Society*, February 9, 1892) that this is the safest guide to the condition of the blood, representing as it does the hæmoglobin value of the individual cell; for the absolute quantity of cells and hæmoglobin varies greatly according as the blood is concentrated by diuresis or diluted by retention of fluid in the body,* but these things cause no variations in the value of the blood decimal, which can easily be represented in a curve, for comparison with that of the urate excreted in the urine.

Fig. 50 represents the results of simultaneous examination of the blood and urine in myself, the blood being examined every two or three days, and the urine curves obtained by dividing the total excretions of three days by three so as to shorten the figure.

Notice the general downward direction of the blood decimal and the general upward trend of the uric acid curve. The urea curve is given simply to show the height of uric acid above urea (the curves are super-imposed at the relation of 1—33) as the index of the probable amount of uric acid passing through the blood.

On May 20, at the beginning of this figure, urea is close to uric acid, so that little or none passed through the blood, and the blood decimal is fairly high—·71. On May 23 uric acid exceeds urea by $1\frac{3}{4}$ grs., and this amount probably passed through the blood, and with this the blood decimal falls to ·7. On May 26 more than 2 grs. of uric acid passed through the blood, and yet the blood decimal rises decidedly to ·78, but the explanation of this is probably that the blood was not examined sufficiently often to correspond with the excretion curves, for uric acid was low on two days preceding the 26th, while a high rise on the 26th brought up the average in the blood for three days to 2 grs. per day. If the blood had been examined on the 25th, it would probably have been found above ·8, a fall to ·78 taking place with the high uric acid on the 26th. The blood is again examined on June 1, the uric acid in it averaging meanwhile 2 to $2\frac{1}{4}$ grs. per day, and with

* See *Journal of Physiology*, vol. xiii., and *Lancet*, July, 1892.

this there is a fall to ·72. On June 10, with uric acid rising to 3¼ grs. per day, there is a marked fall of the blood decimal to ·6; there is a slight rise on the 11th, corresponding to a fall of uric acid; and a fall of the blood decimal to ·56 on the 19th in accordance with the passage of 3 to 3½ grs. through the blood on the days from the 16th to the 19th. Lastly, we see a rise of

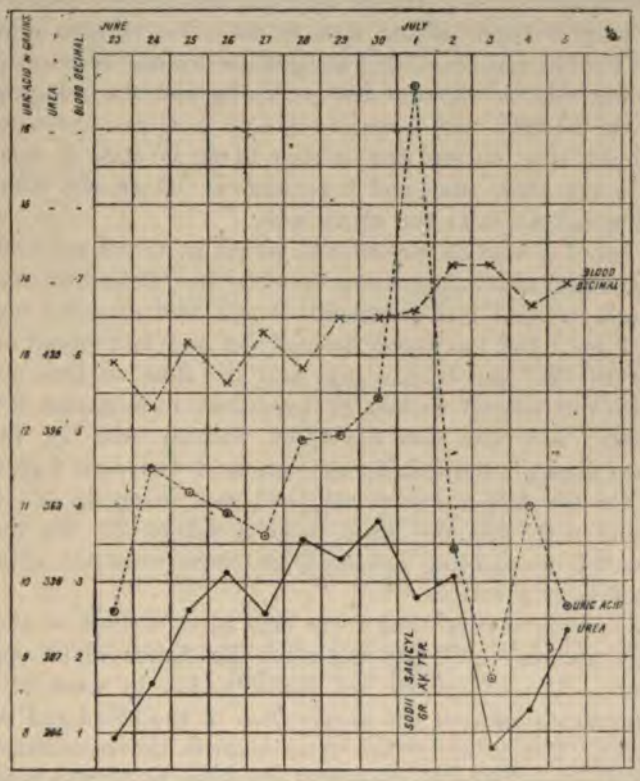

FIG. 51.—CURVES OF URIC ACID EXCRETION AND THE BLOOD DECIMAL FROM DAY TO DAY.

the blood decimal to ·63 on the 22nd, with a fall of the uric acid passing through the blood to 1¼ grs. per day.

This figure shows generally that the blood decimal is higher the nearer the uric acid is to urea, *i.e.*, the less there is passing through the blood; and lower the higher the uric acid is above the urea, *i.e.*, the more there is passing through the blood.

The high rises of uric acid on the 10th and 16th were due to uric acid taken by the mouth to increase the amount passing through the blood.

Fig. 51 shows similar curves of results obtained on myself, the blood being examined every day.

On the 23rd uric acid exceeds urea by 1½ grs. and the blood decimal is at ·59. On the 24th uric acid exceeds urea by 2¾ grs. and the decimal falls to ·53. On the 25th the uric acid exceeds urea by 1½ grs. only, and the decimal rises to ·62. On the 26th uric acid exceeds urea by less than 1 gr., and yet the decimal falls to ·56, but it rises next day to ·63, uric acid remaining still about 1 gr. above urea. On the 28th, with a rise of uric acid to 1⅓ grs. above urea, it falls to ·58, then on the 29th it rises to ·65 in spite of uric acid being 1½ grs. above urea, and it remains at ·65 on the 30th, uric acid being still about 1½ grs. above urea.

On July 1 I tried an experiment, taking gr. xlv. of sodii salicyl., with the object of bringing a large quantity of uric acid through the blood, and in this I was successful, as uric acid exceeded urea by nearly 7 grs.; but the blood decimal did not fall, indeed it rose slightly to ·66. On July 2 uric acid fell close to urea, as the salicylate was left off, so that by hypothesis none passed through the blood; and with this the blood decimal rose to ·72 and remained there on the 3rd, though uric acid was about ¾ gr. above urea. On the 4th, however, uric acid rose, being 2¾ grs. above urea, and with this the blood decimal fell to ·66. On the 5th uric acid fell again, being scarcely ¼ gr. above urea, and with this the blood decimal rose to ·69.

The exceptions mentioned above only serve, I think, to show up the rule that uric acid and the blood decimal move in opposite directions. The exceptions are probably due to want of exact correspondence between the examination of the blood and that of the urine. The urine of the given date is the secretion of the 24 hours ending 7 a.m. on that date, while the blood was examined at 11 a.m. each day. It is quite possible that a large amount of uric acid passing through the blood between 7 and 11 a.m. may depress the blood decimal more than the excretion of the previous 24 hours would lead us to expect, or a small excretion in those same hours might allow the blood to recover a little from the uric acid of the previous day.

That salicylate of soda could bring so much uric acid through the blood without depressing the blood decimal was rather a surprise, but I would point out that these large excretions under

salicylates are not accompanied by the usual symptoms of collæmia. There is no headache, and but little mental or bodily depression, though if 7 grs. of uric acid had passed through the blood in combination with an alkali, there would have been severe headache, marked mental and bodily depression, slow high-tension pulse and scanty urine, and with these probably a marked fall of the blood decimal (as in the case of the lady mentioned above).

The rise of the blood decimal with the low uric acid the day after the salicylates is extremely interesting, and illustrates probably the way in which these drugs did good in the case of splenic leucocythæmia mentioned above, and in cases of simple anæmia and

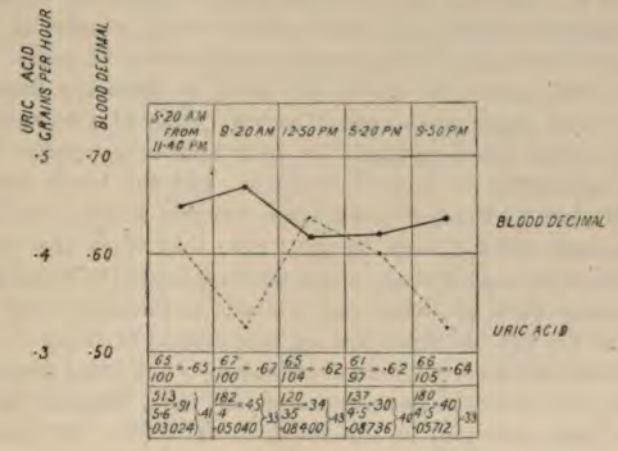

FIG. 52.—CURVES OF URIC ACID EXCRETION AND THE BLOOD DECIMAL FROM HOUR TO HOUR.

chlorosis in which I have also used them, when iron did not seem to act well; for as we shall see presently, uric acid is more powerful than iron, and when both are present in the blood together, its decimal falls instead of rising.

It seems, then, that the good effects of salicylates are due to two things: first, that they clear urates out of the body without allowing them to do harm in passing through the blood; and second, that they, by elimination, free the blood from uric acid and allow the decimal to rise.

In watching the blood decimal curves over long periods of time, as I have often done, and as is shown incidentally in fig. 74, I could

not help noticing what I have mentioned above, that now and again where the uric acid had been low in the previons 24 hours the blood decimal had perhaps not risen as much as one would have expected, or, on the other hand, when uric acid had been high it had not fallen as much as seemed likely from previous experience, and noting these slight variations led me to examine the relations of these curves to each other over shorter periods of time.

And when this was done the cause of these slight variations became apparent, for I found that the blood decimal really varied from hour to hour with the uric acid passing in the urine; hence a large rise of uric acid at the end of the 24 hours period would depress the blood decimal more than the 24 hours curve would lead one to expect, or, on the other hand, a large fall of uric acid for a few hours would cause the decimal to rise in spite of a large excretion of uric acid during most of the previous 24 hours.

Now the curves in fig. 52 are given to illustrate that point. They do not show quite normal curves, either of uric acid excretion or of the blood decimal, for uric acid is generally high at 9 a.m. and lower at noon and 5 p.m., and the blood decimal is generally low at 9 a.m., rising again towards 1 p.m., but they do show exactly what I want to point out, that when the uric acid excretion is unusually small in the morning hours the blood decimal is unusually high, and when the uric acid is unusually high in the middle of the day the blood decimal falls instead of rising.

If there had been only one examination of the blood decimal, say at 9.20 a.m., it would have appeared too high, because there had been a large excretion in the previous 24 hours; but examining more closely, we see that on this particular morning the uric acid excretion fell very much from 5.20 a.m. to 9.20 a.m., so the blood decimal rose above its usual level at those hours, and also above what one would have expected from the excretion of the previous 24 hours as a whole.

The figures below the curves in fig. 52 are 65 per cent. hæmoglobin over 100 per cent. of cells, and the resulting decimal = ·65, and below these 513 the total urine in cc. divided by 5·6, the time in hours, and giving a resultant 91 cc. per hour; below these is ·03024, the percentage of uric acid in the urine, and this × 91 = ·41 grs. of uric acid per hour, as indicated in the curve.

But the excretion of uric acid is under complete control, and being altered from hour to hour at pleasure the blood decimal will follow, so that any desired curve can be produced, and I will undertake to alter the blood decimal curve of anyone in either

direction, or if I am allowed to examine the blood of anyone every two or three hours, I will tell correctly the chief variations in the excretion of uric acid in the urine over the same period.

In an interesting paper in the *British Medical Journal*, 1898, vol. i., p. 1650, Dr. W. Edgecombe refers to Dr. Oliver's Croonian Lectures of 1896, and gives further observations of his own to show that there is a normal day and night rise in the worth (= blood decimal) of the blood, that active exercise increases the day fall and the night rise, while rest diminishes the day fall. And

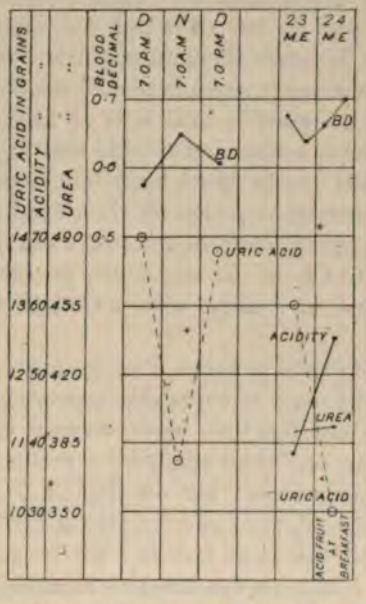

FIG. 53.—THE BLOOD DECIMAL CURVE SHOWING THE ORDINARY DIURNAL VARIATIONS, THEIR RELATION TO THE EXCRETION OF URIC ACID, AND THEIR REVERSAL BY REVERSING THE EXCRETION OF URIC ACID.

his conclusion is that rest is of considerable value in the treatment of anæmia.

I was interested in his facts, though I could not accept his explanation, for I knew that the blood decimal, as we have seen in fig. 52, follows the uric acid excretion from hour to hour, and will consequently fall during the day, when there is much uric acid in the blood and urine, and rise during the night, when there is little, and that it was the amount of uric acid in the blood and not the rest or exercise *per se* that affected the blood quality.

But this article made me test the point for myself, and finding that the statement was quite correct, and that the blood decimal was, as a rule, higher in the morning and lower in the evening day after day, I then proceeded to diminish the excretion of uric acid in the day to see whether I could produce a corresponding alteration in the blood curve, and one of the results I thus obtained I give in fig. 53.

To the left of the figure are the normal results obtained by separating the urine into three consecutive periods of twelve hours, 7 a.m. to 7 p.m. and 7 p.m. to 7 a.m. The lower curve is the excretion of uric acid in two days and one night, the totals being multiplied by two to make them comparable with the twenty-four hour curves, and the upper curve is that of the blood decimal.

The uric acid excretion is thus seen to have been about 7 grs. during the day twelve hours, and a little over $5\frac{1}{2}$ grs. in the night twelve hours, or $12\frac{1}{2}$ grs. in the twenty-four hours; and the blood decimal in correspondence with this rises from the evening to the morning and falls from the morning to the evening.

To the right of fig. 53 we see above the blood decimal curve, and below it those of acidity, urea and uric acid on two days, 23 and 24.

On day 23 uric acid is above urea by nearly 2 grs. and there would consequently be a fair quantity passing through the blood, and with this we see that the blood decimal falls as usual from morning to evening, and rises again from evening to morning, just as in the previous curves; but on day 24 I purposely brought down the excretion of uric acid by taking freely of acid fruit at breakfast, in much the same way as I did to alter the circulation curves in fig. 39; and we see the rise in acidity I produced and its effect in the fall of uric acid, which on this day is considerably below urea, and with this the blood decimal rose during the day instead of falling.

In another series of experiments I gave alkalies at night, with the result of increasing the excretion of uric acid in the night hours, and diminishing, more or less decidedly, the rise in the blood decimal that usually takes place in those hours, but I shall not take up further space by giving the curves here.

Dr. Edgecombe's observations that exercise increases the extent of the day fall is not difficult to explain, for we see in figs. 46 and 47 and context that exercise increases the amount of uric acid passing through the blood, and thus just reverses what I did in day 24 of fig. 53, with the reverse effect on the blood decimal.

Dr. Edgecombe also shows in an interesting way that if night is turned into day the fall then occurs in the night, as he gives curves from the blood of a hospital nurse, first on day and then on night duty; and he points out, what is also interesting, that the falls at night when on night duty are less than the falls in the day when on day duty, no doubt because the exertion gone through on night duty is less than that on day duty.

On night duty the excretion of uric acid is greatest at night and least in the day, because food and exercise are all altered, and the blood decimal will here, as elsewhere, move in the opposite direction to uric acid.

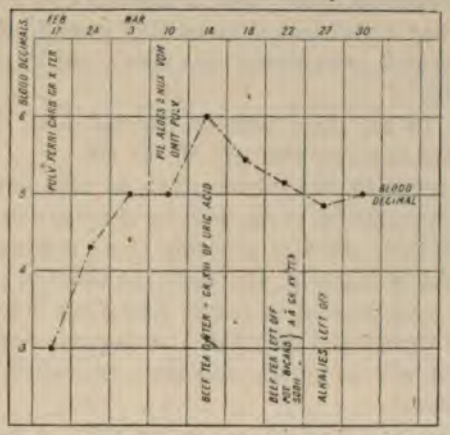

FIG. 54.—CURVE OF BLOOD DECIMAL IN CHLOROSIS SHOWING EFFECTS OF IRON, BEEF-TEA, AND ALKALIES.

I will say in conclusion that these and other experiments have left in my mind no doubt that the blood decimal not only fluctuates from hour to hour, and day to day, and season to season, with the fluctuations in the excretion of uric acid, but that it can be made to alter in any direction at pleasure, just as the blood granules and the excretion of uric acid in the urine can be altered and controlled. The fluctuations in the blood decimal are a perfectly reliable guide to the daily, weekly or monthly changes in the uric acid in the blood and urine, so that an estimation of the blood decimal may take the place of the more troublesome or often impossible collection and estimation of the urine, and even an approximate estimation of the blood decimal by the colour card, which I have produced for the purpose, and shall mention later on, will give valuable information not otherwise obtainable.

I shall now go on to other figures, showing some of the results I obtained in cases of chlorosis by causing excess of uric acid to pass through the blood. In these the urine was not collected, but no doubt the effects on excretion were the same as in my own case, and the administration of uric acid in one form or another always produced distinct effects on the blood decimal.

Fig. 54 shows the curve of the decimal in the case of M. B., aged 18, suffering from chlorosis. On February 17, the decimal being only ·3, she was put on pulv. ferri carb., gr. x. ter, and the curves show the rise of the decimal to ·5 on March 10, and its further rise to ·6 on March 14, after the iron had been left off. On the 14th half a pint of beef-tea three times a day was added to her diet, and this beef-tea was found on estimation to contain about 8·6 grs. of uric acid to the pint; she would thus take about 13 grs. of uric acid or xanthin a day.

On March 18 the blood decimal has fallen to ·54, and on the 22nd, when the beef-tea was left off, to ·52.

Uric acid given by the mouth to those who, like anæmic girls, have rather low nutrition, is more likely to remain in solution in the blood, because their blood is probably more alkaline than that of better nourished individuals; therefore the effect of giving uric acid is likely to be more marked in poorly nourished individuals than in those who are robust and well fed, and dose for dose the effect on the blood curve will be greater and more immediate in the former than in the latter.

Though I stopped the beef-tea on the 22nd, I gave bicarbonate of potash and soda, 15 grs. of each, three times a day, with the object of increasing the urate in the blood, and we see on the 27th that the blood decimal has further fallen to ·48. The alkalies were then left off, and on the 30th the blood decimal had risen slightly to ·5.

I have no doubt that the whole of this fall was due to the uric acid taken, for the general tendency is for the blood curve to rise slowly for a considerable time after the iron is left off.

Fig. 55 is the blood curve of E.E., aged 23, also suffering from chlorosis. On May 4, her decimal being at ·35, she was put on pulv. ferri carb. as in the previous case. On May 26, the decimal having risen to ·56, the iron was left off. On June 2, when the decimal had risen to ·57, she was given beef-tea = 13 grs. uric acid per day, and this was continued till the 8th, the blood decimal falling on the 5th to ·54 and on the 8th to ·53.

On the 12th, four days after the last dose of uric acid, the blood

decimal had risen again to ·55. On this day, the 12th, she was put on the equivalent of 6 grs. uric acid for one day and 3 grs. each for the two following days, to try the effect of smaller doses, and on the 15th the blood decimal had fallen again to ·53, so that the effects of a small dose were fairly marked, and a small dose will, perhaps, get uric acid into the blood more quickly than a large one, for uric acid interferes with its own solubility; and the salts contained in beef-tea will in a similar way tend to depress the alkalinity of the blood and cause the uric acid to be stored in the fibrous tissues and viscera instead of remaining in solution in the blood; and in producing changes in the blood decimal, we have not only to get it into the blood, but to keep it there so long as the kidneys will allow it to remain unexcreted.

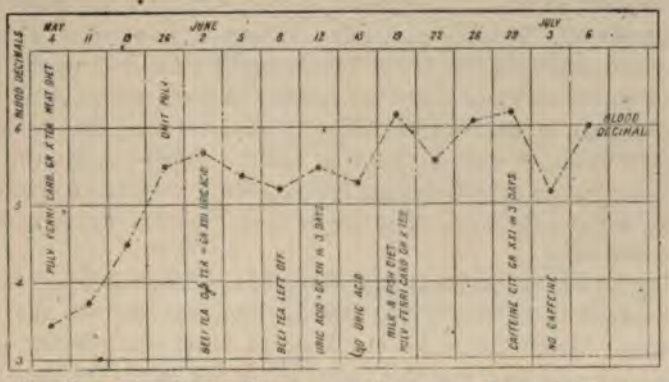

FIG. 55.—CURVE OF BLOOD DECIMAL IN CHLORISIS SHOWING EFFECTS OF IRON, BEEF-TEA, AND CAFFEIN.

On the 19th there is a remarkable rise of the blood decimal to ·62, making it look as though it would have gone on rising all the way from June 2 but for the uric acid taken.

On the 19th iron was again given in the same dose as before, and it was rather a surprise, therefore, to find that on the 22nd the blood curve had fallen to ·57, but I had forgotten the fact that, on the 19th, the patient was not only put on iron, but also on a milk and fish diet, having previously been on meat, and the change of diet produced a fall of acidity, acting like the alkali given in the previous case; this brought some of the previously stored uric acid through the blood, and this overcame the iron, and produced a fall in place of a rise in the decimal.

A similar explanation can be given of a point in fig. 54 which I omitted to mention. In this figure it will be seen that on

March 10 the decimal failed to rise, though the iron was still being taken, and this, I think, was the result of some abdominal pain and digestive disturbance which were unfortunately produced by some aloes pills given her for constipation ; the digestive disturbance no doubt produced collæmia, and the uric acid, as in the other case, overcame the iron so far as to prevent a rise of the blood decimal.

By the 26th, however (fig. 55), most of the uric acid has passed through the blood and been excreted; the iron then comes into action and the blood decimal rises to ·61. On the 26th the iron is left off, but the decimal again rises on the 29th to ·62.

On the 29th citrate of caffein was given, 9 grs. on the first day, and 6 grs. on each of two subsequent days. Now caffein may for all practical purposes be regarded as uric acid, and my experiments on myself (fig. 29) show that, like uric acid, it first raises the acidity and clears uric acid out of the blood, causing freedom of capillaries and a diuresis; later, when the acidity falls, an excess of uric acid, proportional to the caffein taken, passes through the blood and into the urine ; * and we see that caffein brought down the blood decimal, just as uric acid does, for on July 3 we have a marked fall to ·52, which is followed by a rise to ·6 on the 6th, the drug having been left off.

Fig. 56 shows the blood decimal of J. K., suffering from chlorosis. From April 11 to May 7 she was on iron, and we see the rise it produced in the decimal. On May 11 iron was left off, and on May 15 the decimal was the same as on the 8th. On May 15 and two following days the equivalent of 4 grs. of uric acid was given; on May 18 the decimal had fallen, but it rose again on the 22nd and 25th, after the uric acid had been left off. However, on the 17th and 18th menstruation was present, and as this might have caused a fall of the blood decimal I repeated the dose of uric acid on the 25th and two following days, and on the 29th the decimal had again fallen, to rise again on June 1, after the uric acid had been left off.

There seems to be very little doubt that the administration of uric acid and its passage through the blood (for a similar administration to myself does cause it to pass in excess through the blood into the urine, figs. 24 to 29) causes a distinct fall of the decimal in spite of the presence of a considerable amount of iron in the body.

But iron does not always succeed so well as it did in this case,

* See also Prof. See, *Lancet*, 1900, vol. i., p. 677.

and then, as we shall see in the following case, it fails because it is unable to clear the blood of uric acid, for other drugs which have more power in clearing the blood of uric acid succeed. Fig. 57 shows the blood decimal of A. P., aged 17, suffering from chlorosis, and below this for comparison I have placed the curve of the urine excretion in ounces.

She had been attending as an out-patient for full three months, and taking iron the whole time, but on February 27 there was no improvement; the gums were very pale, and the face puffy and wax-like.

I took her in, examined the blood, and found the decimal at 0·34. I put her on pulv. ferri carb., and on March 6 the blood decimal was just the same; so that a week on iron and in bed produced no

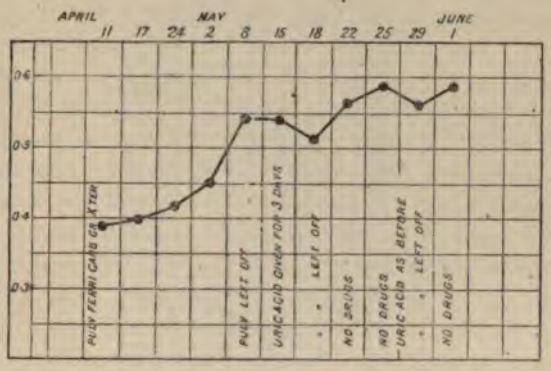

FIG. 56.—CURVE OF BLOOD DECIMAL IN CHLOROSIS SHOWING EFFECTS OF URIC ACID.

improvement. She suffered considerably from headache and dyspepsia, and I have little doubt that the dyspepsia kept the acidity low, and prevented the iron from clearing the blood of uric acid; hence, though given steadily for three and a half months, it had done no good.

To test this point I began to examine the urine, and on March 8 there were 29 oz. containing 267 grs. of urea and 15·2 grs. of uric acid, a relation of uric acid to urea of 1—17. On March 9 there were 28 oz. of urine containing 206 grs. of urea and 13 grs. of uric acid, relation 1—15.

Here, then, while the patient was on iron we have evidence of a great excess of uric acid in the urine, and no doubt also in the blood, which explained her headache, scanty urine (for the urinary

water is in everyone inversely as the uric acid excreted along with it), and her œdematous, almost myxœdematous, face, caused by retention of fluids in her tissues, besides completely explaining why the iron had failed to do good.

On March 10, however, there was a slight improvement, and the blood decimal had risen to 0·37, but as I had found such an excess of uric acid in the urine in spite of the iron, I decided to stop it and give a drug which I knew had more power of clearing uric acid out of the blood and urine. I accordingly put her on the ordinary mist. hydrarg. perchlor c. pot. iod. three times a day, and the rest of the figure shows its effect on the blood and urine.

On March 13 there were 39 oz. of urine, containing 304 grs.

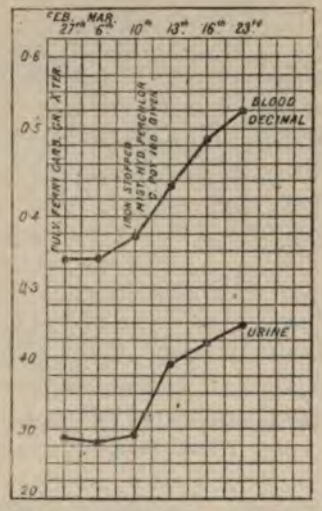

FIG. 57.—CURVE OF BLOOD DECIMAL IN CHLOROSIS SHOWING EFFECTS OF IODIDE OF MERCURY.

of urea and 10·8 grs. of uric acid, relation 1—28. Note the increase of water and urea and the decrease of uric acid in illustration of the law above mentioned.

On March 16 there were 42 oz. of urine, containing 232 grs. of urea and 9·1 grs. of uric acid, relation 1—25.

On March 23 there was 45 oz. of urine, containing 332 grs. of urea and 9·7 grs. of uric acid—relation 1—34, or normal.

And with this clearance of the blood and urine of uric acid the blood decimal went up by leaps and bounds, and having risen in eleven days on iron only ·03, it rose ·06 in three days

on iodide of mercury, and ·15 in thirteen days, reaching ·53 on March 23, a height to which more than three months on iron had quite failed to raise it; and we now know why, for the one drug cleared the blood of uric acid and the other failed to effect this result. I know, however, from experience in other cases, that even the iodide of mercury may fail to clear the blood and urine of uric acid, and then, like iron in the above case, it also fails to produce any continuous improvement in the decimal.

The marked rise in urinary water, which coincided, as it always does, with the equally marked fall in uric acid, soon removed the excess of water from the tissues, and her face assumed a natural appearance, her appetite and digestion improved, and she considered herself cured. After what we have said in chapter x. it is most interesting to note the disappearance of the dyspepsia with the clearing up of the collæmia, the latter being in this case the chief cause of the former.

But for the dyspepsia the iron would have been able to clear out the uric acid at first, and then she would have been cured in six or eight weeks instead of remaining almost unaffected at the end of three months. Now it is well known that Murchison and others have pointed out that in some cases iron will not cure anæmia till the liver has been got into proper order, and the drug he used to get the liver into order was mercury (see Murchison, "Croonian Lectures," *Lancet*, 1874, vol. i., p. 504; and fig. 17, chapter iii.). We can now see that this mercury did good, not by any special action on the liver as was supposed, but because it cleared the blood of uric acid, and so altered at once the circulation and nutrition of the whole body; and any other drug that clears the blood and urine of uric acid produces the same rise in excretion of urea, but some have more power, and will succeed in clearing the blood of uric acid when others have failed, and mercury (as we have seen in chapter viii.) is independent of nutrition and acidity.

I was much interested to hear Dr. Dundas Grant say at a meeting of the Hunterian Society (*Lancet*, 1897, vol. i., p. 1275), that chloride of ammonium is not only useful in headache, but is a hæmatinic, and had been recommended as such by Dr. Barnes and others; for we have here one more substance which clears the blood of uric acid, and improves its condition by doing so; here also is the explanation of the relief it affords in headache, neuralgia, and hepatic congestion, for it produces a free capillary circulation and a fall of blood pressure. I have already pointed out with reference to sp. ammon. aromat. that ammonium salts raise the the acidity of

the urine, and I shall have to point out later that they do harm in acute rheumatism; but in the chloride we have not only the ammonium, but a powerful mineral acid also introduced into the body. It is interesting to note here one more instance of the great general law that precipitants do good in collæmic diseases and solvents do good in precipitation diseases, and *vice versâ*. The precipitant ammonium does good in collæmia and anæmia, harm in arthritis; alkalies do good in arthritis, harm in collæmia and anæmia.

Chloride of ammonium is a well-known precipitant of uric acid outside the body, and, as we have seen, it is possible by means of the microscope to watch its effects on the uric acid and xanthin in the blood itself.

On the other hand, you have only to introduce into the body and blood an excess of uric acid to quickly undo all the good that iron, mercury, salicylates, or anything else has done, which still further emphasises the fact that they do good merely by clearing the blood of uric acid. If you give uric acid along with iron the decimal falls, or at least fails to rise further, so long as the uric acid is continued, which parallels what we have just seen in Nature, that when there is a great excess of uric acid in the urine and blood, iron may be administered for months without effect.

In the *Lancet*, 1895, vol. i., p. 769, it is said that sulphate of copper is far better than iron for the treatment of anæmia, and the dose recommended is $\frac{1}{3}$ to 1 gr. twice a day; this dose is much smaller than that of iron, but larger than that of mercury in the mixture given in fig. 57, but, like iron and mercury, copper is well known to form an insoluble compound with uric acid. I have myself used copper in the treatment of chlorosis with results quite as good as those with iron.

I may say at once that these and similar experiences have left no doubt in my mind that just as iron runs up the blood decimal uric acid brings it down; and that when the one is acting in opposition to the other the uric acid is the more powerful.

But as soon as the blood is cleared of uric acid, the general metabolism, being freed from the incubus of obstructed capillaries, goes ahead, dyspepsia vanishes and there is a general rise of urea and acidity, which keeps the blood more or less clear of uric acid for some time, whether the iron is continued or not.

I have every confidence that I can in this way do anything I like with the blood decimal, and that anyone who will repeat my experiments will get similar results.

In addition to the figures given above, I have examined my own blood and urine side by side every day for many weeks, and find that the changes are practically constant, and that with every marked rise of uric acid excretion the blood decimal falls and *vice versa;* and, indeed, I would undertake to tell correctly, from a daily examination of the blood of a patient, whether the uric acid had risen or fallen each day, the urine being examined by someone else.

To conclude this part of the subject, I will show a small figure, No. 58, which proves that others have obtained results identical with my own, without knowing how they were produced.

In the *Journal of Physiology*, vol. xv., I suggested that extracts of thyroid and other glands possibly owe no small part of their activity in myxœdema and skin diseases to the stimulant properties of the uric acid and other nitrogenous extractives in which they are known to be rich; and I can prove that in myself the taking of thyroid gland or a thyroid extract produces results which are identical with those produced by so much uric acid (see fig. 30). There

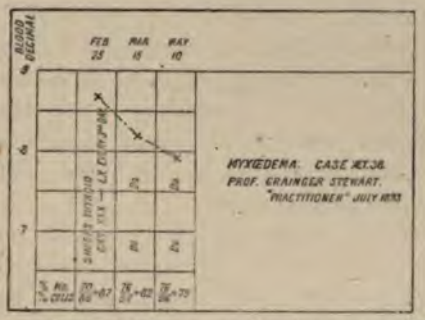

FIG. 58.—CURVE OF BLOOD DECIMAL IN MYXŒDEMA SHOWING THE EFFECT OF THYROID FEEDING.

is a first stage of stimulation with rising acidity, well-being, free capillaries and diuresis (just as with caffein also), followed later, when they are left off, by falling acidity with plus excretion of uric acid, obstructed capillaries and scanty urine, and with these latter a fall in the blood decimal, just as with uric acid taken in other forms.

It is interesting to note in this connection that myxœdema, like asthma, Raynaud's disease, and dropsy, is better during pregnancy or fever, and we shall have an instance of the effects of the fever of measles on the dropsy of Bright's disease in chapter xiii. Again, myxœdema, like certain skin diseases, may be worse at the men-

strual periods, while arthritic troubles, which stand at the opposite pole of causation, tend to be worse during fever and may be better during menstruation (see *Lancet*, 1893, vol. ii., p. 744; *British Medical Journal* Epitome, September, 1892, p. 43, and *ibid.*, February, 1892, p. 25).

I was therefore much interested to see in the *Practitioner*, July, 1893, a paper by the late Professor Sir T. Grainger Stewart, in which he gives the blood factors in a patient who was being fed with 30 to 60 gr. of thyroid gland every third day for myxœdema.

Fig. 58 shows the blood decimal curve constructed from the figures which he gives, and demonstrates that this feeding with thyroids produced a steady fall of the blood decimal. It is true that the red cells rose from 80 to 96 per cent., but this is simply due to concentration of the blood; for thyroid gland, as I have said, just like uric acid and caffein, may cause diuresis (see fig. 30); the hæmoglobin, however, did not rise proportionately, and on the last occasion it did not even rise absolutely, so the result is a steady fall of the blood decimal, doubtless due, as in my own curves, to an excess of uric acid passing through the blood.

Professor Stewart's patient also suffered from the symptom of an excess of uric acid in the blood, such as weakness and general soreness, with tightness and oppression in the chest, passing later into severe dyspnœa, with blood-stained expectoration, her asthmatic trouble being complicated by the presence of old disease of the mitral valve (see chapter ix.).

It is now easy to understand the causation of chlorosis and anæmia, and their relation to dyspepsia and bilious attacks, for these disturbances cause excess of uric acid to pass through the blood; but there are other most interesting relations between the development of girls and the causation of these troubles which furnish at least some explanation of the frequency with which anæmia is met with in young women.

We have seen that uric acid obstructs the capillaries throughout the body and thus diminishes the formation of urea and the production of animal heat; and we shall see in the next chapter that the fall of urea it produces is contemporaneous with the presence in the blood and urine of an ill-metabolised and diffusible albumin; and that when we give drugs that clear the blood of uric acid the urea increases just in proportion as the diffusible albumin diminishes. In a word, the urea which does not appear in the urine is accurately represented by the diffusible albumin which does, and by altering the amount of uric acid in the blood, and so controlling circulation,

metabolism, and combustion, we can make the one give place to the other.

It is clear, then, that uric acid controls the results of many metabolic processes, and determines the properties of some constituents of the blood; and we have only to extend this power to the corpuscles to understand the phenomena both of paroxysmal hæmoglobinuria and anæmia; they and all their relatives are results of defective metabolism, which again, just as in the case of fatigue, is the result of defective circulation.

In the *Lancet*, 1904, vol. ii., p. 1560, there is an interesting paper by Dr. H. Batty-Shaw on "The Relation of Splenic Anæmia of Infancy to other forms of Blood Diseases Occurring in Infancy and Childhood," and towards the end he says: "It is more in harmony with recent investigations to insist upon the close relationship of all blood diseases, anæmias, primary and secondary, and leucocythæmias, rather than to attempt to separate them at the bedside as sharply defined groups." He further says: "Pathological considerations do not at present justify the recognition as separate diseases of what are really merely different degrees of reaction of the blood-forming tissues to various excitants, the nature of which at present is obscure." My researches lead me to agree absolutely with these statements, made, as they have previously been, by Raynaud and others I have quoted (see chapter xi.), and I can name with certainty one of the excitants, and that is uric acid, for not only has no one who swallows uric acid as good blood as those who abstain from it, but the blood quality varies from morning to evening with the amount of uric acid passing through it, and can be made to vary at any time in either direction by adding or withholding uric acid from the food.

There is also an interesting article in the *Lancet*, 1906, vol. i., p. 1466, by Dr. A. G. Banks, who narrates the history of a case of "Hæmorrhagic Purpura during Convalescence from Scarlet Fever," and he is inclined to think that the causation of this is practically identical with that of the albuminuria or Bright's disease which more often follows scarlet fever. The interesting bearing of this upon what I have already said about blood diseases and the causation of purpura, and shall have further to say about the production of Bright's disease, needs no pointing out. An excess of uric acid in the blood may be, under slightly varying conditions, the cause of either the one or the other, and the train of events which leads up to such troubles in sequence to scarlet fever is easy to understand.

And now as to the causation of chlorosis. It will, no doubt, be readily admitted that we meet with it chiefly in women between the ages of 16 to 25. How do girls and women of these ages differ from boys and men of the same ages? As you know well, a girl at about the thirteenth year develops with enormous rapidity, and her weight may increase by as much as 11 lb. in this one year, as she dashes at a bound from childhood into womanhood.

Now, this very rapid development entails a corresponding rapidity of tissue change and a large formation of uric acid and urea per pound of body weight—this being always greater in the child than in the adult. But high urea formation is always accompanied by high acidity, that is to say, the urine will be highly acid and the blood lowly alkaline. The blood alkalinity being low, it will be but a bad solvent of uric acid, and hence a considerable proportion of the urate formed in these years of active metabolism will not be held in solution and excreted, but will be retained and deposited in various parts of the body, giving local signs of which we shall speak presently.

The same applies to the uric acid of introduction, if the girl is fed on flesh and tea, &c., the nitrogenous metabolism being large and active, the alkalinity of the liver will be low, and a great part of the introduced uric acid will be retained.

Unfortunately, later on a girl's metabolism falls greatly, and by the end of the eighteenth year her increase of weight is almost *nil;* with this there is a fall in the formation of urea and of acids, and the blood becomes more alkaline; as a result it becomes also a better solvent of uric acid, and it now takes up and passes into the urine as much uric acid—probably several hundred grains—as was stored in the tissues during the preceding period of active metabolism, from 12 to 14. Hence, from 16 to 19, or later, she will have an excess of uric acid passing through her blood, and will suffer from its effects on the blood decimal—namely, chlorosis.

To illustrate this point a little further, I give in fig. 59 a curve showing the annual increase in weight of boys and girls.* From this we see that the greatest development in girls is in the thirteenth year, and in boys not till the sixteenth; and though the boys' curve falls very greatly in the seventeenth and eighteenth years, they are still increasing about 5 lb. a year when the curve ends.

Now, girls in their more early development will probably form more uric acid and urea per pound than boys in their later development, and when later on the girls' increase is almost *nil*, the uric

* Copied from a paper by Dr. W. Stephenson, *Lancet*, September, 1888.

acid previously retained will pass through the blood both in greater quantity and more suddenly than it does in boys, whose increase is for several years later very considerable and their acidity not so low. I have therefore added to Dr. Stephenson's curves a line representing the probable effects of the girl's increase in weight on the formation of urea and acids, and a broken line below showing

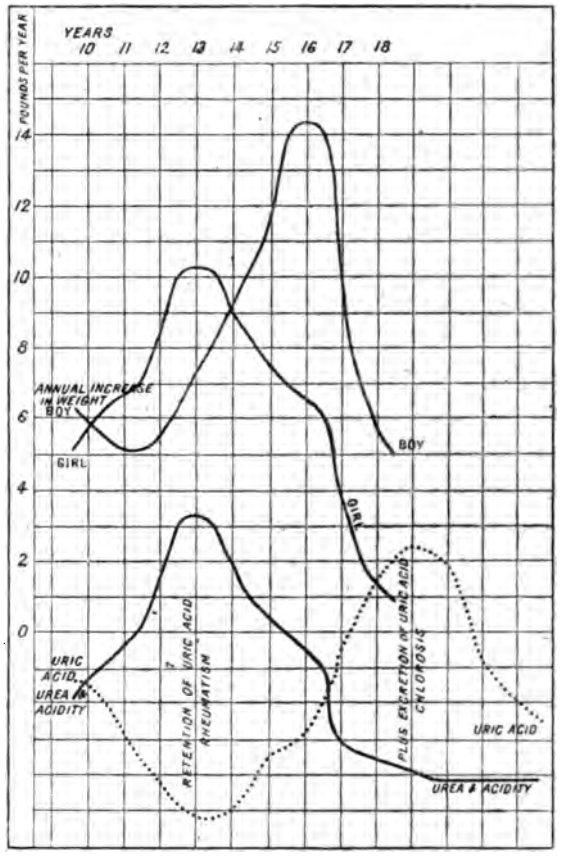

FIG. 59.—CURVES SHOWING DEVELOPMENT IN BOYS AND GIRLS AND ITS EFFECT ON THE EXCRETION OF URIC ACID.

the effect of this on the excretion of uric acid, and from these we see at a glance that the chlorosis and anæmia of 18 are the result of the passage of an excess of uric acid through the blood, which again is the result of a previous storage of this substance from 12 to 15. Add to this that just at the time when a girl's increase

of weight is coming down and her urea and acidity falling, menstruation is established; and even if this does not upset digestion and appetite, it often obliges girls to keep quiet for several days, so that its result is to still further reduce urea and acidity, and still more markedly flood the blood with uric acid, thus completely accounting for the increase of chlorosis and the functional troubles met with at menstrual periods (see also stages of life mentioned on p. 236).

Dr. Luff (*Lancet*, 1897, vol. i., p. 946) thinks that there is no uric acid in the blood of men and animals in health, and I have already quoted Professor von Jaksch's observations showing that he found none in a few cases; but Sir A. Garrod, it may be remembered, did find some in healthy blood ("Gout and Rheumatic Gout," 3rd Ed., p. 113).

I differ from some of these observers merely in thinking that a small quantity is present in the blood of man even in perfect health, and that there is more at some hours of the day and less at others, as shown by the changes in the blood itself and the corresponding changes in the excretion in the urine (see fig. 52), and, indeed, the results just shown in the previous figures are absolutely inexplicable if an excess of uric acid in the urine does not mean a corresponding excess of uric acid or of xanthin in the blood.

The blood changes can, as we have seen, be produced by swallowing either uric acid or xanthin, which are chemically so closely related (see Lea, "Chemical Basis of the Animal Body," p. 174); but the conditions which control the excretion of this substance in the urine correspond at numerous points with the known solubilities of uric acid and not with those of some of the xanthins; and as I have already pointed out in chapter i., eating of meat has been found by very numerous observers to increase the excretion of uric acid in the urine, while the xanthins are present in that fluid only as mere traces; and yet meat, like tea, coffee and cocoa, introduces into the body little or nothing but xanthin, which is therefore, we must conclude, converted into uric acid.

Again, I agree with all these observers in finding some uric acid in the blood in disease; and not only so, but my observations are in complete accord with those of Professor von Jaksch and Sir A. Garrod, as I have found most in the blood in exactly the same conditions as they have found most, and have shown that the quantity rises and falls in these conditions in exact accordance with the factors affecting its solubility, which are practically identical both for physiology and pathology. Again, in several pathological

conditions, as leucocythæmia on the one hand and acute rheumatism on the other, the quantity in the urine is known to correspond with that in the blood; and if this holds in pathology it is difficult to see any reason why it should not hold also in a minor degree in physiology.

The condition of the blood itself also varies in pathological conditions just as in physiological or artificial ones, with the quantity of uric acid in the blood and urine (see figs. 57 and 74).

Dr. Luff, I believe, does not tell us in how many cases he examined the blood, nor does he tell us what, from my point of view, is still more important, the hour at which it was drawn, as I should only expect to find it in quantities that could be identified in any blood that could reasonably be drawn from a living man at some hours of the day; and even at alkaline tide hours, accidental variations, as shown, for instance, in fig. 52, might cause it to appear to be absent, so that a large number of results carefully published, with full details as to time of day, food, exercise, drugs, and conditions of the subject, would have to be produced to prove absence of uric acid from normal blood, and even then it would be necessary to give some other explanation of my physiological and pathological results, which can be reproduced to any extent.

It seems also to be quite unnecessary to postulate, as Dr. Luff does (*Lancet*, 1897, vol. i., p. 944), an altered condition of the renal epithelium to account for the accumulation of uric acid in gout, when the excretion of this substance varies from hour to hour with the acidity of the urine, and can be made to vary to almost any extent by administration of acids and alkalies; and why, if this substance does not come from the blood, does the blood show corresponding changes?

Again, as we shall see in the following chapters, an extremely diseased kidney may yet excrete a great excess of uric acid, and we have already seen that a perfectly normal kidney may, in conditions of low alkalinity of the blood, excrete very little.

As to the presence of uric acid in the blood of birds I see that Dr. Watson has published some results (*British Medical Journal*, 1899, vol. i., p. 205) showing that he found undoubted evidence of uric acid in the blood of birds.

And this has a special interest for me, for when I showed the process of Mr. Barker Smith for precipitating urate granules in the blood (see p. 90), at a meeting of the Royal Medical and Chirurgical Society in March, 1898, Dr. Luff, who objected to my saying that the test was one that demonstrated the presence of uric acid in the

blood, brought forward the fact that the granules were present in the blood of birds as conclusive evidence of the small importance of the granules, because, as he had shown, there was no uric acid in the blood of birds.

I must leave him to settle the point with Dr. Watson, but meanwhile my further researches have shown conclusively that the granules in human blood are uric acid or xanthin, and that I have absolute and complete control over the number in which they are present in the blood stream, a control co-extensive with that over the quantity of uric acid in the urine.

Again, if we look at this figure (59) we shall see that we have got not only a complete explanation of the causation of chlorosis, but have also come upon an equally complete explanation of the girl's great tendency to rheumatism as compared with her brothers, for I have for years been pointing out* that what we call gout or rheumatism is really the irritation of certain joint structures by uric acid or urates retained in those structures; and that they are retained in those structures by the same causes (namely, a rise of acidity or the presence in the blood of any substance whose urate is insoluble) that prevent their excretion, and bring about their retention in the body in general.

Now the retention in this instance is produced by a rise of acidity, and the joints are one of the places in which the urate is retained; it is little wonder, then, that girls are specially liable at this period of their lives to acute rheumatism, and Dr. Cheadle says† that girls of 10 to 15 years old are twice as liable to rheumatic fever as boys of the same age, these years including, I remark, the period of their most active metabolism.

But we already know that migraine and rheumatism alternate, and we have recorded on p. 463 a quotation from Dr. Liveing which says that a woman became subject to megrim *after puberty;* now fig. 59 tells us exactly why her trouble came at that time as well as why epilepsy and chlorosis tend to originate at the same period.

With retention of uric acid there is arthritis; but with plus excretion and excess of uric acid in the blood, which comes later, there is no arthritis, but headache, epilepsy, mental depression, chlorosis and anæmia; there is low blood pressure and quick

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* *Practitioner*, February, March, and April, 1891, and *British Medical Journal*, July, 1888.

† *Lancet*, vol. i., 1889.

capillary reflux with the first series (arthritis), and slow capillary reflux and high blood pressure with the second (the collæmic series).

Probably boys are liable to rheumatic fever from a similar cause at 16 years of age, but their active metabolism coming when they are older, they form less uric acid per pound than girls; and further, they probably retain much less uric acid at this time owing to their more active habits of life.

For it follows from our first principles of urate excretion that, other things being equal, those in any given period of life retain most uric acid in their body who take least exercise, and those retain least uric acid in their body who take most exercise, which explains Cullen's well-known observation that gout seldom attacks those employed in constant bodily labour (see figs. 46 and 47).

No one will deny that boys take much more exercise than girls all through school life, and especially as compared with girls at and after the commencement of menstruation. We see, then, that boys differ from girls in that their active metabolism comes later, when their formation of uric acid per pound is smaller, and that, owing to their greater bodily activity, they retain a smaller amount of the uric acid they form; while, lastly, their activity and nutrition are better continued and maintained, and they are not subjected to the depressing effects of menstruation, so that any urates they have retained pass more gradually through their blood; hence they escape more or less the chlorosis and anæmia from which their sisters suffer.

But if a boy at this time of life meets with an accident which lays him up and cripples his bodily activity and nutrition, he will then probably suffer from anæmia much as a girl of the corresponding age, and many of the over-fed boys of our great public schools show, for a time at least, about 17 and 18, a more or less marked tendency to anæmia.

Paroxysmal hæmoglobinuria represents, I have no doubt, a similar but more acute fluctuation in the excretion of urates, probably often related to dyspepsia and gastric upset in exactly the same way that migraine, epilepsy and Raynaud's disease are related to it, and it is paroxysmal just as they are paroxysmal, in relation to the fluctuations in urate excretion.

Anæmia associated with enlarged spleen is doubtless related to the large quantities of uric acid met with in the blood and urine of these cases (see pp. 461 and 483).

The way in which the excess of uric acid in the blood is brought about I have already gone into; and as said above, the increase of white cells met with in these cases may be secondary.

In the *Practitioner*, August, 1890, Dr. F. W. Mott wrote an interesting paper on the spleen as a centre of destruction of red cells, and it may be noted in this connection that Dr. Hunter (*Lancet*, 1892, vol. ii., p. 1318) points out that certain substances (toluylene-diamine), which have a destructive action on the blood, act less powerfully after the spleen has been removed; and no doubt if uric acid destroys the blood elements, they are certain to meet it in concentrated solution in the spleen, and the facts just mentioned suggest strongly that the action of toluylene-diamine is indirect. This also suggests that in the case of splenic leucocythæmia mentioned above the salicylates did good by clearing the uric acid out of the spleen.

The effect of fevers in producing anæmia is easy to understand, for they diminish the alkalinity of the blood and lead to a storage of urate in the body, and this, when the fever ends, finds its way back into the blood (see facts about Pneumonia, chapter iii.), causing post-febrile collæmia with post-febrile bradycardia, high tension pulse, depression of mind and metabolism and subnormal temperature, an identical sequence of events with those producing chlorosis. The excess of uric acid in the blood and urine after malaria and other fevers, with or without enlarged spleen, is thus, I believe, the result of the storage of urate that took place during the fever (compare also previous remarks on Rheumatism in Girls).

In vol. lxxxv. of the *Transactions of the Royal Medical and Chirurgical Society*, Dr. Garrod has an interesting paper on the anæmia of rheumatism and the relation of the blood changes to the excretion of uro-hæmatoporphyrin.

In several of his curves "worth," which corresponds with my blood decimal, remains steady or rises during the fever, and falls afterwards as the temperature becomes subnormal, that is to say, during the fever the urate is all in the joints, and there is none in the blood except in combination with salicylates (see previous remarks on the Action of Salicylates in Anæmia); as the fever passes off there is post-febrile collæmia with a fall of the blood decimal, just as we should expect when urates combined with alkali are passing through the blood; and in at least one of Dr. Garrod's cases the "worth" fell at the end of the fever *in spite* of iron being given (see also Dr. Garrod's remarks, previous reference, p. 191).

He also notices a corresponding increase of white corpuscles, just as in the similar condition mentioned above, and as observed by Dr. Wheaton (chapter xi.).

The effect of all fevers on the blood decimal is probably the same as that of acute rheumatism, and I found in a case of pneumonia that at the time of the post-febrile collæmia with subnormal temperature the blood decimal was ·55, while a few days later, after the temperature had again gone up to normal, it had risen to ·6.

I have now for some time been watching with interest the relation between the raised temperature of a febrile disease with its quick capillary reflux and low blood pressure, and the subnormal collæmic temperature with slow reflux and high blood pressure that follows it.

And to avoid details and a long line of figures I may say shortly that their relation is nearly 1—1, that is to say, for every day of raised temperature in the fever there will be one day of subnormal temperature after it comes to an end. But in those who were full of urates before the fever the subnormal temperature may be greatly prolonged, with corresponding depression and anæmia.

This is well seen in short sharp fevers such as pneumonia, less well in chronic fevers, such as enteric, where the temperature drags along often for days just above the normal.

In a more chronic fever with debility, though the temperature is from 99—100, the debility allows the alkalinity of the blood to rise, the capillary reflux is inclined to slow and the blood pressure to rise, and in these days towards the end of the fever there is no retention of uric acid, but rather a plus excretion.

Hence, to reckon those days as part of the fever would put out the relation of 1—1. This also explains an observation made by the late Dr. Mahomed that you may get a pulse tracing showing high blood pressure in spite of a slightly raised temperature near the end of a fever.

We may express this result another way by saying that the store of uric acid begins to overflow before the end of a long fever if there is debility, which allows the alkalinity of the blood to rise.

In the following case salicylates were given early in the fever and perchloride of mercury towards the end, with the result that the salicylate swept out some of the uric acid and diminished retention in the fever, and the mercury prevented to some extent the excretion of urates after it, the result of the two actions being that the days of subnormal temperature bore a relation to those of fever of only 1—2. .

The temperature chart is that of a child admitted into the Metropolitan Hospital on July 6, with pneumonia of the left apex. It was given salicylate on the 6th, but it had to be discontinued on the 10th, owing to some vomiting. From the 6th to the 10th the temperature rose from 102° to 105°. On the 13th, as it had some diarrhœa and offensive motions, it was given bismuth and liq. hyd. perchlor., which were continued till the 24th.

The temperature fell on the 19th from 103° to 100°, and on the 20th it was between 97° and 98° for two-thirds of the day; on the 21st it touched 98° for four hours, on the 22nd it did the same, and again on 25th and 29th, and was below 98° for parts of July 31 and August 1. The rest of the time it was steady, about normal, or from 98·4° to 98·8°.

There were here at least fourteen days of fever, and during the next fourteen days the temperature only touched 98° or went below it on seven days.

I believe that by giving salicylates all through a fever the days of subnormal temperature that follow can be reduced; in the above case the salicylate could not be given all through the fever, and part of the reduction of subnormal temperature was due to the mercury which was given later on.

It is easy to explain the effects of hot weather and of tropical climates in producing anæmia, for heat increases the alkalinity of the blood and the urate it will hold in solution; and this will have most effect in those who eat meat and drink tea, and least in those who live on a uric-acid-free diet (see chapter xvii.).

The effects of diet also are well known and easily explained, for Dr. Mackenzie points out that meat diet increases the destruction of red cells (*Lancet* or *British Medical Journal*, 1891, vol. i.), and others have pointed out that farinaceous diet does good, and that pale, anæmic children are most common among the "well fed" upper classes (*British Medical Journal*, 1890, vol. ii., p. 85)—in my opinion, "not wisely, but too well" fed upper classes.

The paper which immediately precedes mine on anæmia in the *British Medical Journal*, 1893, vol. ii., p. 670, is one with the heading "Preliminary Report on the Causes of Chlorosis," by E. Lloyd Jones, M.D., and contains many points of interest, and many of which the causation by uric acid will be found to give an explanation.

Thus, he points out that after 15 years of age the specific gravity of the blood falls in the female, while it continues to rise in the male, and that this is the age at which girls become anæmic.

But if this anæmia and chlorosis are results of excess of uric acid in the blood, the causation of which at this time of life I have already gone into, it is not difficult to see that this collæmia entails a fall in the specific gravity of the blood, because it prevents the outflow of water from it by any or all the glandular organs of the body.

It is easy for anyone to convince themselves in two or three hours' work that this is a fact; let them produce in any of the ways previously described so much collæmia as shall markedly diminish the excretion of water in the urine, and watch the blood meanwhile; they will find that hour by hour as the urinary water diminishes, the water in the blood increases; that is to say, there is a relative diminution of both cells and hæmoglobin in the given quantity; conversely, when they clear uric acid out of the blood and produce a diuresis, they will find that the relative quantities of cells and hæmoglobin return to the position they held before the experiment.

I have come to believe that I can tell from the concentrated or hydræmic condition of the blood whether there has or has not been a diuresis produced by any drug given; and as you cure chlorosis there is a rise in the urinary water, and the patient loses weight from diminution of the blood and tissue fluids (see fig. 57). No doubt hydræmia goes with all anæmia, for the excess of uric acid which causes the defective blood metabolism and anæmia must at the same time and in the same way cause retention of fluids in the body.

I look, therefore, upon the fall in specific gravity of the blood of the female which takes place at 15 as the result of collæmia, which produces in the ways sketched out both hydræmia and anæmia, and this is itself the result of her very active metabolism at 13 coming to an end, and of her menstruation establishing itself.

As the male is not exposed to these great fluctuations in metabolism with the collæmia they produce, he does not show corresponding blood changes. His metabolism goes more steadily ahead, and he lives also, be it observed, at this time of his existence, a much more healthy life than his sister.

I do not believe that there is any "natural tendency" either to a fall in the specific gravity of the blood or to chlorosis; they are simply results of our meat-eating and tea-drinking habits, and of our civilisation.

If our girls did not take so much meat, meat extracts and tea they would not store so much urate, and would suffer less from

arthritis in their time of active metabolism at 13, and if at 15 they led the life of healthy active savages, instead of resting, lying up and becoming semi-invalids, there would be none of the present great fluctuations in their metabolism, but as in the case of their brothers, their development would go more steadily ahead, there would be no falling urea and acidity, no collæmia, and, consequently, no hydræmia and anæmia.

Further on, Dr. Jones seeks to establish a connection between chlorosis and disturbance of splanchnic innervation with dilatation of gastro-intestinal vessels, and he goes on to say, "This I conceived to be brought about in a reflex manner, and this appeared to me to be the more likely since I had met with some cases in which the usual gastro-intestinal disturbance, together with marked chlorosis, had rapidly followed a shock or chill—generally a shock or chill occurring about a menstrual period." Exactly so, and causing, therefore, a great fluctuation in the excretion of uric acid and the amount passing through the blood (see figs. 31 and 32).

The very constant relation of chlorosis to gastro-intestinal disturbance, bilious attacks, and chronic dyspepsia is most marked, and the way in which such dyspepsia will often for weeks and months prevent iron from doing any good and curing the chlorosis is with me a frequent experience in the out-patient room, so that my rule is to treat the dyspepsia, or the iron will have no chance. Nature is here merely repeating the experiment that was performed for us in fig. 54, where the digestive disturbance produced by a pill put a temporary stop to the rise of the blood decimal under iron.

It is only necessary to keep up dyspepsia to ensure collæmia, as there is plenty of available uric acid in the body in these cases; and I believe it would be quite possible, by giving a gastro-intestinal irritant, such as colchicum, and at the same time administering xanthins in food or drugs, but in larger quantities than I used in the previous figures, to produce most severe, even fatal, anæmia, and many facts suggest that not a few of the cases called pernicious anæmia have this origin.

They come at a time of life when from years of wrong diet there are large accumulations of uric acid in the body, and any chronic gastro-intestinal irritation supervening at such a time must produce more or less severe collæmia and anæmia. Up to a certain point all such anæmias are curable by any treatment that will relieve the gastro-intestinal condition and make it possible for other drugs to clear the blood of uric acid; but once debility becomes great and

appetite and nutrition fail, it is practically impossible to clear out the uric acid with any drug, and the disease is fatal.

Before leaving the subject of anæmia, it may be useful to give a short summary of the facts.

First, then, by the clinical observation of paroxysmal hæmoglobinuria, Raynaud's disease, splenic leucocythæmia, chlorosis and anæmia, and the relation of many of these troubles to "bilious attacks," dyspepsia, menstruation, cold, heat, fever and drugs, I was led to believe that there was an important connection between the blood changes and an excess of uric acid in the blood and urine. As to these facts, I am at one with other observers, but differ from them as to their meaning and causation.

Secondly, there is my observation that the value of my blood decimal alters from day to day, even from hour to hour, with the amount of uric acid passing through it, and that if intentional variations are produced in the uric acid, the blood decimal follows suit.

I believe also that my blood will generally compare very favourably with that of other men of my own age who eat more animal food than I do. Indeed, I rarely see anyone with blood as good as mine, except patients who have been on my diet for four or five years.

There are practically no meat-eaters and tea-drinkers whose blood is up to my highest standard, or whose capillary circulation is as quick as mine, and when uric-acid-free dietists and meat-eaters are together it is easy to pick out the latter by their slow capillary circulation and relative anæmia.

Thirdly, there is my observation that all the above facts hold good for others also, and especially for anæmic and chlorotic patients, and that the blood decimal can be lowered by administering uric acid.

Lastly, we see that the knowledge thus acquired enables us to explain the chief points in the causation of these diseases.

Thus I believe that many whose professional experience goes back thirty or forty years would agree that chlorosis is much more common now than formerly, and hence I was interested in the remark of a woman among my out-patients at the Royal Waterloo Hospital, who said with reference to her daughter's chlorosis, "Ah, sir, we never used to see this sort of thing when I was young." Now, if her observation is correct as to the facts, what has happened in the thirty or forty years of her recollection? Why, agriculture has been ruined and the people driven more and more from the country into the towns, where they have aped the meat-eating and

tea-drinking habits of their social superiors, and increase of chlorosis is one of the results. But even in country towns they are now pale, as observed by me in a visit to Carlisle, but Carlisle has a public abattoir, of which it is proud, and, curiously enough, the next object of interest on the list (B.M.A. membership card, 1896) was the human cemetery, humanity itself being the cemetery of the animals, as I believe to its infinite hurt.

I have mentioned above that one of the blood changes met with in paroxysmal hæmoglobinuria is an increase of coagulability: and several things seem to render it probable that if uric acid thus directly or indirectly increases the coagulability of the blood, it may exercise an important influence in the pathology of thrombosis.

The frequent clinical connection between thrombosis and gout or diabetes, of both of which I shall have something to say presently, is too well known to need more than mention; and a similar relation is often found between thrombosis and certain post-febrile and puerperal conditions; the thrombosis of enteric fever is also an incident of the post-febrile collæmic period; and after what I have already said about these, I need hardly insist on the fact that one point common to all these conditions is the frequent presence of excess of uric acid in the blood; again, unless my clinical observation deceives me, thrombosis is not very uncommon in Bright's disease, and in this disease (as we have seen in chapter iii.) the researches of Professor R. von Jaksch confirm my own in showing that an excess of uric acid is frequently found in the blood (*Centralbl. für inn. Med.*, May 23, 1896).

In the *Lancet*, 1894, vol. i., p. 1446, is the record of a case of thrombosis following an attack of influenza, and said to be due to the breaking up of white blood cells. I think it more probable that it was due to post-febrile collæmia which followed the influenza, and that the increase of white cells and increase of coagulability were, just as in paroxysmal hæmoglobinuria, the results of the collæmia (see previous remarks on this and on Splenic Leucocythæmia).

From this point of view also I was very greatly interested in Sir J. Fayrer's article on "Intravascular Coagulation and Pulmonary Thrombosis" (*British Medical Journal*, 1893, vol. ii., p. 165), for in many of the conditions which he mentions, such as malaria, splenic disease, puerperal conditions, hot damp weather (see also Causation of Fatigue, figs. 46 and 47), and especially surgical operations in hot damp weather, there is no doubt that a great excess of uric acid would often be present in the blood.

I shall mention in chapter xiv. the effects of surgical operations in increasing the excretion of uric acid and urea, and, combined with hot weather, these would greatly increase the quantity of uric acid passing through the blood.

Again, I noticed in the *Lancet*, 1896, vol. i., p. 475, a case of fatal pulmonary apoplexy in a girl of 14 years, which came suddenly after a walk just at the end of a perfectly normal monthly period; but here we have at least three causes of collæmia, the exercise, the menstruation, and the girl's age, referred to in fig. 59. Similarly, a case of pulmonary thrombosis recorded in the *British Medical Journal*, 1896, vol. ii., p. 1504, coming after enteric fever, is said to be due to debility, and here again, I think, we must not forget post-febrile collæmia.

Lastly, if, as I have suggested (chapter v.), colloid uric acid mechanically obstructs the capillaries, and if from time to time small portions of this obstructing substance are carried past the capillaries into the veins, we can at once see how they may come to form nuclei of thrombosis, if the colloid is not dissolved as the blood gets warmer in the deeper tissues.

So that this colloid mechanical theory may help us to understand the observed connection between gout and thrombosis.

And once a coagulum has formed round such a nucleus, it will not dissolve even in the warmest parts of the central circulation, though the colloid uric acid alone may completely disappear there. I have also seen some wonderful recoveries from phlebitis on uric-acid-free diet.

Then there is another point among the symptoms of paroxysmal hæmoglobinuria, of which I am now able to give an explanation. It will be readily admitted that in the urine of paroxysmal hæmoglobinuria oxalate crystals are very frequently present; let us enquire further as to their meaning.

In the *British Medical Journal*, 1885, vol i., p. 167, Sir T. Lauder Brunton points out that when sulphuretted hydrogen is allowed to act on a concentrated solution of urates, oxalate of lime is produced; now, in the urine of paroxysmal hæmoglobinuria we have undoubtedly a concentrated solution of urates, for I have demonstrated both the facts and their causation over and over again; we have probably also sulphuretted hydrogen in this urine, and the point of greatest interest is the way in which this sulphuretted hydrogen is produced.

Sir T. Lauder Brunton points out that the sulphuretted hydrogen, which produces the oxalate crystals in the urine, is

generally formed in the intestines during digestion of cabbages and other food rich in sulphur, and the way in which it comes to be produced in the intestines in the paroxysm of hæmoglobinuria is a point of great interest.

In chapter vii. I have pointed out, in answer to the arguments of Messrs. Herter and Smith, of New York, on the causation of epilepsy, that the intestinal putrefaction of which they noticed so many signs in this disease was the simple and constant result of an excess of uric acid in the blood; and I argued that the excess of urate in the blood which obstructed all the capillaries and raised blood pressure to the extent of interfering with the intracranial circulation and producing the fits, would interfere also with gastro-intestinal digestion and absorption and allow putrefactive processes to take their place. I doubt not also that a precisely similar explanation may be given of the excess of bacteria in the intestine and the poison found in the urine as a result of their activity in cases of pernicious anæmia (see Dr. Hunter, *Lancet*, 1891, vol. i., p. 260). Dyspepsia, often severe dyspepsia, is a very constant symptom of pernicious anæmia, and it follows from what I have been saying that all dyspepsia is a cause of collæmia and anæmia, which are more severe and lasting the larger the amount of the available uric acid. Here also the uric acid in the blood is the first thing, while the bacteria in the intestines, and any products they may generate, are secondary and, as in the parallel case of epilepsy, unimportant (see also a paper on "Hydrothionuria" in the *New York Medical Journal* of June 17, 1892). This in many cases accompanied digestive trouble or disease, and it is said that it (sulphuretted hydrogen) may also be formed by bacteria in the urine.

Messrs. Herter and Smith say (previous reference): "We cannot say why there should occur in epilepsy so considerable a proportion of cases in which there are evidences of excessive intestinal putrefaction." To my mind the explanation seems simple; and I suggest that a similar explanation can be given of the presence of oxalates in the urine of hæmoglobinuria, for here also we have collæmia and general obstruction of capillaries, and while the excess of uric acid is causing the blood destruction, the obstructed capillaries suspend gastro-intestinal digestion, and putrefaction, doubtless with the formation of more or less sulphuretted hydrogen, takes its place. Some of that sulphuretted hydrogen passes with the excess of urates in the concentrated urine, and the frequent presence of oxalate crystals in this fluid is thus explained. Lastly, the explanation

throws backwards a most interesting light on the actual causation of paroxysmal hæmoglobinuria, and demonstrates that it is contemporaneous with the presence of an excess of uric acid in the blood and urine, and deficient circulation in the intestines, which we cannot see, as well as in the skin and extremities, producing the symptoms of Raynaud's disease, which we can see, and which are well known to be so frequently associated with it (for a case in which sulphuretted hydrogen was formed in a dilated stomach see *Centralb. für inner. Med.*, December, 1894).

From this point of view I have been interested in an article in the *British Medical Journal*, 1905, vol. ii., p. 1663, on "Toxic Cyanosis of Intestinal Origin," in which it appears that cyanosis may be due to the absorption into the blood of decomposition products from the intestines, and that the effect of this is to cause methæmoglobinæmia and sulph-hæmoglobinæmia, from which it appears that this interesting condition is but an exaggeration of that described above which produces oxaluria. I have myself seen one case probably of this nature, though the doctor who had been attending on it considered that it was due to an overdose of tar products used in treatment. The patient had all the most marked signs of collæmia, anæmia and migraine, and in addition to these there was a general cyanosis of all the structures. I unfortunately saw this case before the interesting article above mentioned appeared in the *Journal* or I should have drawn the blood and examined its condition. But no doubt the collæmia which produces oxaluria by producing absorption of sulphuretted hydrogen generated in the intestines, may also, if somewhat more chronic and continuous, suffice to explain these changes in the blood.

It is most interesting to note that in some of these cases the urine was found to be rich in indol and scatol, and that these substances were progressively diminished when the patient was put on milk diet, but returned again when a mixed diet was given, thus beautifully illustrating its real origin, which is not, as the author concludes, in the intestines, but in the uric acid in the circulation, which conditions and determines the decomposition in the intestines. I have seen several cases where darkening of complexion, almost sufficient to suggest Addison's disease, has cleared up on a uric-acid-free diet prescribed for other reasons.

Dr. Hunter (*Lancet*, 1903, vol. i., p. 367) mentions three or four points of which uric acid causation enables me to give an explanation. Thus, speaking of twenty-five cases observed in the last three years he says, "the average age was 51 years," and this, I remark,

is just near the end of the middle life retention period and the beginning of the old age collæmic period, therefore just at the most favourable time for severe collæmia and its effect, anæmia (see chapter v.).

Again he says, "*Sex:* nineteen cases were in men and six were in women." The explanation of this is again simple, for men retain most in the middle period of life, as women excrete a considerable amount at each monthly period. And those who retain most in the retention period of the prime of life will have the most severe collæmia in the decline of life about and after 50.

Again Dr. Hunter says, "*Station in life:* there were seventeen private patients and eight hospital patients." Here again the private patients no doubt put in more meat foods, tea and coffee, and hence had more collæmia than their poorer brethren.

And most interesting of all he says, "*Gastric or intestinal disturbance:* a history of antecedent gastric or intestinal disturbance, as I shall presently show, was found in every case. In no case were these of sufficient character or intensity to account for the supervention of such an intense degree of anæmia."

Can anything be more simple than the explanation of this relation? Dyspepsia is the one thing wanted to bring all the stored uric acid through the blood, and of course the anæmia is not proportional to the dyspepsia but to the amount of uric acid available, and so to the severity of the collæmia which dyspepsia produces.

This leaves on my mind no doubt that pernicious anæmia will own to a causation identical with that of other forms of anæmia, and I have records of several cases which others have called pernicious anæmia, and which yet cleared up completely on correct diet, sometimes without other treatment.

In the *Lancet*, 1903, vol. ii., p. 1419, is an interesting article on the "Anæmias of Infancy," by Dr. Clive Riviere, in the summing up of which he says, among other things, "These are not specific blood diseases, but owe their peculiarities merely to the 'infancy factor,' and they represent merely different stages of the same condition." "The common cause of severe anæmia in infants is gastro-intestinal catarrh leading to the absorption of toxins, either from the growth of micro-organisms, or possibly from the formation of poisonous by-products of digestion."

Here again there is no difficulty in understanding the meaning of this pathology, for given an individual who either directly or through its mother has imbibed a large quantity of uric acid, there is nothing more certain than that gastro-intestinal catarrh may result (as a

rheumatism of the intestines from exposure to cold), and this catarrh, when produced, will flood the blood with uric acid, which again will result in more or less anæmia, according to the quantity of uric acid available. Gastro-intestinal trouble of one sort or another, flooding the blood with uric acid, is a very constant factor in all forms of anæmia, and there is a still more marked relation between serious gastro-intestinal trouble and the more fatal forms of anæmia. In the debate on Dr. Riviere's paper at the Royal Medical and Chirurgical Society, there were at least two cases mentioned by those who spoke, in which mercury had produced marked improvement. Mercury here acted just as iron and all other things (metals, acids and salts) that have ever been found to cure anæmia, simply by clearing the blood of uric acid.

Precisely the same remarks apply to the discussion on the "Pathology of Splenic Anæmia," recorded in the *British Medical Journal*, 1903, vol. ii., p. 573, and it is acknowledged by Professor Hamilton, p. 581, that "The pathology of this, as of many other blood diseases, is wrapped in obscurity, though he is inclined to think that the investigation of possible intestinal toxins constitutes a promising line of enquiry." I know one line which is still more promising both for the patient and the investigator; and uric acid, as appears in this volume, is at once the cause of the intestinal toxins and of the anæmia, and nothing is to be gained by investigating one consequence while seeking for the cause of another.

Diagnosis.—Anæmia associated with excess of uric acid in the urine, and probably scanty urine, as in the case of A. P., fig. 57, and associated with these will probably be dyspepsia, dysmenorrhœa, heavy work or other cause of excessive fatigue, *i.e.*, causes which tend to bring excess of uric acid through the blood whenever such excess is available in the body; thus what is called a "heavy place" is a common contributing cause of chlorosis in servant girls, and we already know the relations between fatigue and collæmia.

When anæmia occurs in such association with excess of uric acid in the urine and blood, we can treat collæmia with full confidence of success, for we know and can demonstrate that the collæmia is the cause of the blood changes, and not, as was previously supposed, their result.

I believe that all forms of destructive blood changes and anæmia are due to uric acid, and that when this poison has been successfully shut out of the diet in childhood such diseases will cease to appear.

I should not despair of curing any case where there was a

reasonable chance of being able to clear the blood of uric acid; but the chief things that tend to make that chance a small one are incurable gastro-intestinal disease, great enlargement of the spleen, which mechanically and otherwise interferes with digestion, and long continued and severe debility in those no longer young, especially if in previous years they have swallowed large quantities of uric-acid-containing foods, *e.g.*, flesh and tea.

For treatment we must as far as possible reverse the conditions that produced the trouble and remove the causes of excessive fatigue or dyspepsia.

But if diet clears the blood of uric acid (1) by stopping introduction at once, and (2) by allowing the gradual elimination of the uric acid already in the body, we ought to be able to cure chlorosis by diet alone without any drugs like iron, which directly clear the blood of uric acid, but provide also for an almost certain relapse, in that they do not remove the uric acid from the body, but store it up in the tissues, and it is matter of common knowledge that chlorosis so treated does relapse again and again.

I now show in fig. 60 the results of an attempt I made to do this in the case of a girl of 16 under my care in the Metropolitan Hospital.

At the beginning of the figure her blood decimal was found to be slightly above ·3, and she presented all the ordinary signs of chlorosis. She was put on a milk diet with a little fish, and no drugs.

Her blood decimal remained at exactly the same level in the two following weeks, in spite of nursing and rest in bed, and then on November 28 the fish was left off.

On December 5 there was a decided fall in the decimal, and the patient had begun to suffer from headache, both being, no doubt, the result of the passage of some excess of uric acid through the blood; I would refer to a similar fall in the blood decimal produced by a similar change of diet, *i.e.*, from meat to milk and fish in fig. 55 (June 19 to 22, and remarks on this). No doubt the change from meat to fish and milk produced a fall in the acidity of the urine and allowed the passage of some excess of uric acid through the blood, and similarly in fig. 60 the leaving off of fish produced a fall in the urinary acidity and so some excess of uric acid in the blood and a fall of the blood decimal, the same result being further indicated by the onset of headaches.

The blood decimal recovers a little on December 12, but fails again on the 19th and 26th, the headaches continuing in spite of an

acid mixture, and then it steadily rises to the end of the figure, the headaches being much less frequent and severe by January 2, and some salicylates being taken in conjunction with the acids on January 9 and onwards.

My object in giving this figure is to show that the first effect of leaving all animal food out of the diet is a fall in the decimal, and this is due to the passage through the blood of some of the excess of uric acid in the body, and this is further shown in this particular case by the onset of headaches; we may note also that as the headaches got less the blood decimal steadily improved.

This patient went on for some months beyond the end of the figure slowly improving; then she began to lose weight slightly, and it was found that she was not taking her milk and farina-

FIG. 60.—CURVE OF BLOOD DECIMAL IN CHLOROSIS SHOWING THE EFFECT OF A URIC-ACID-FREE DIET.

ceous diet well, and so she was put back on to ordinary diet and given iron, under which she improved more quickly, and in a few weeks was able to go out.

I remark with regard to this that the quickest way out of chlorosis is to give iron, mercury, copper, zinc, or any other drug that directly clears the blood of uric acid, but then a relapse is a matter of certainty, a longer or shorter time (generally within six months) after the metal is left off.

To cure entirely by diet, however, is, as shown in the above case, often very tedious, and there will probably be a more or less decided fall of blood decimal at first, which may lead to complaints on the part of the patient and her friends; the cure, however, though slow, is certain, and there is no relapse.

I believe, however, that the best way to treat chlorosis is to combine the use of diet and drugs in the following way:—

When the patient first comes under treatment give ordinary diet, remove dyspepsia if present by means of bismuth and sodii bicarb., with a saline (sulphate) purge if there is constipation, and then go on to give any of the above metals, it matters little which; I got just as good results with copper or iodide of mercury as with iron. I regard the mercuric salt as the most powerful,* but then there is the chance of iodism, mercurialism, and intestinal irritation; the copper also may cause colic and intestinal trouble. Or mercury may be given as pil. hydrarg. in small doses along with iodides, chlorides, and bromides, as advised in the next chapter in the treatment of Bright's disease, and in cases of that disease so treated the blood decimal always improves as the albumin diminishes and the urea increases, *i.e.*, as the combustion is freed from collæmia. Iron is probably the least powerful as regards the blood, but it is less liable to cause gastro-intestinal trouble than the others.

When the blood decimal has been got up to ·5, ·6 or above, give salicylates, say every alternate week for six or eight to clear out the uric acid, and towards the end of this time reduce and leave off all flesh foods, altering the diet to that advised in chapter xvii. The patient is now well, and as long as she remains on a uric-acid-free diet will continue to be so.

Thus Ellen W., aged 23, was under my care in the spring of 1896 in the Royal Waterloo Hospital suffering from relapsing chlorosis; after treating her with iron as in the preceding figures, I let her go out after showing her my diet and telling her that if she would take care to follow it she would not have any further relapses.

She returned as an out-patient on February 18, 1897, on account of some little dyspepsia, due apparently to her eating a large amount of baker's bread, and suffering in consequence from constipation. She told me that ever since she left the hospital she had been doing as I told her, and living (though not quite as I told her) on nothing but bread and milk. But her blood was a picture; I have never

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* For a record of a case of severe anæmia successfully treated by injection of bichloride of mercury and bichloride of quinine, see *British Medical Journal* Epitome, 1896, April 11, p. 59; and for a case of pernicious anæmia similarly treated with mercury and cured see the same journal, 1896, Epitome, July 18, p. 11.

seen such blood in a woman of her age, and she said that all her friends remarked on her fine colour.

Here, then, we have both constipation and dyspepsia existing with magnificent blood, and the reason is simple: there is no uric acid in the body, and there has been no introduction in her food, and therefore dyspepsia cannot bring it through the blood.

I have also heard from Dr. Mackie, of Nottingham, and others, of interesting and successful results in the treatment of anæmia in young women by applying my suggestions as to diet.

I have recorded the improvements in my own blood that resulted from leaving off meat, and later from leaving off all animal food except milk and cheese; and in every case where I have altered the diet for headache, epilepsy, mental depression, or similar troubles, there has been a distinct improvement in the condition of the blood as one of the results. This generally shows distinctly about the end of the first three months, and is greater at the end of six, nine and twelve months, till at the end of twelve to eighteen or twenty-four months a blood which was at first under ·4 reaches my own level, ·7, and above up to ·8, and these people have, and continue to have, a deep rich colour in their tongues and gums which no meat eater can equal, and I often meet people who think their blood colour good till they compare it with mine.

In many cases there is a fall of the blood decimal, as in fig. 60, on first going on to the diet, but this will vary with nutrition, and will be less marked where this is good and is adequately maintained on the new diet, and more marked where, as in the case of fig. 60, nutrition is poor and not well kept up on the new diet.

Then during this primary fall of the blood decimal, if the patient suffers from headaches they will be worse, if from fits they will be more frequent and severe, and mental depression will increase, so that both patient and doctor may become disheartened and give up the diet. But to be forewarned is to be forearmed, and by looking carefully after nutrition this primary fall may be diminished, and as regards headache, fits and depression, it is but one more proof that they are due to the uric acid in the blood, and that patient perseverance in clearing it out and keeping it out will be crowned with success.

These experiences have led me to suggest that in the treatment of headache, fits, mental depression, &c., by diet it is well to examine the blood every few weeks, or oftener, so as to have a guide to the effects of the diet on the excretion of uric acid and the amount passing through the blood; such weekly examination will do practi-

cally as well as a more frequent examination of the urine. And to facilitate this I have now produced a card for the approximate estimation of the blood decimal.* On this is a series of colours, and under each is the probable blood decimal that would be found in a case when the tint of the tongue, conjunctiva or gums approximates to that on the card. This card affords a definite standard of reference and a means of estimating whether much or little uric acid is passing through the blood; in the former case the decimal falls, in the latter it rises.

The capillary reflux will best tell us the hourly and daily fluctuations of uric acid, the blood decimal will give us the record of the balance of fluctuations over weeks and months.

The colours on this card have the numbers ·8, ·6, ·4, and ·2 under them, and it is necessary to add to these ·3 to make them comparable to the ordinary standards of blood quality; thus ·8 becomes 1·1, ·6 is ·9, and so on. This ·3 is arrived at in the following manner: ·15 of it is accounted for by the fact that the blood quality of those who have lived for some years on a uric-acid-free diet is by this much above the recognised standards, and the top colour is an artist's copy of the gums of a successful patient. The other ·15 is due to the fact that the standard of colour comparison which I was making use of at the time I made the investigations for this card is too dark as compared with the present standard by about this quantity. The colour of the standard was supposed not to alter, but as a matter of fact it had darkened with age. A different standard is now used which does not alter in colour. The figures in this book obtained with too dark a standard must also have ·3 added. Thus ·7 becomes 1·0, and ·2 becomes ·5, &c. It has not been possible to alter all the figures in the book, but this explanation will put matters right.

Since the last edition of this book in 1903 I have come upon one case in which a doctor might possibly have entered for the reward I offered in the preface of that edition of £5 for every meat eater whose colour and circulation would equal my own, and the following is the record given me by my friend, Dr. E. G. Horder, under date August, 1903. He had been visiting a sanatorium where the patients were fed up on enormous quantities of beef, beef-juice, and milk, and his friend, the proprietor of the sanatorium, said to him, "You should come here for a few weeks and let me

* To be obtained from Messrs. Bale, Sons, and Danielsson, Ltd., 83-91, Great Titchfield Street, W. Price 1s. each.

feed you up. What you want is meat." Dr. Horder, however, declined the invitation, but a little later the doctor resident at this sanatorium was desirous of some help in the study of the blood, and Dr. Horder gave him some help with regard to this, and eventually they fell to testing each other's blood with Gowers's hæmoglobinometer. The resident was a strong, sturdy man of 28 or 30, living in the open air on beef and milk with the patients at the sanatorium. His blood, on examination, came out at 80 per cent., that of Dr. Horder—who had been several years on uric-acid-free diet—95 per cent. The resident was astonished at the result, and so were two students who were looking on at the discomfiture of the meat fetish, and when they recovered their breath the resident said to Dr. Horder, "How is it done?" and Dr. Horder replied by pointing to himself and saying, "Milk," and by then pointing to the resident and saying, "Meat."

He goes on to remark that this resident had a pulse of extremely high tension, so that even if he had been eligible to compete for the prize on the score of blood condition he was clearly not so on that of circulation, and would be easily beaten by a uric-acid-free dietist of a few years standing.

Anæmia is to-day an all-pervading feature of life in London; it is seen on all sides in marked and increasing severity, except in young children who are not so much dosed with animal flesh and tea, and whose active metabolism keeps their blood for a time free from the poisons. Let a child get ill, however; his fires burn lower and collæmia catches him also.

This general anæmia has just as much to do with the atmosphere of a great city, absence of oxygen, and the wear and tear of modern life, as it has with the mountains of the moon.

It has everything to do with the increasing consumption of animal flesh and the drinking of tea, soups, meat juices and extracts, and this will one day be proved beyond all doubt by the results that will follow a reversal of these habits.

In this chapter we have been dealing with troubles due to collæmia found in association with slow capillary circulation, subnormal temperature and many granules in the blood. Such troubles are therefore relieved by precipitants, but in curing chlorosis, for instance, with precipitants we often produce a precipitation trouble, viz., arthritis; but diet begun early in life will prevent both the collæmic and precipitation troubles and thus render drugs unnecessary, and diet begun early in life is always more satisfactory and successful than that begun later.

CHAPTER XIII.

Albuminuria and Bright's Disease.

One of my first papers on the uric acid headache (*Practitioner*, March, 1886) ends as follows: "And further, as it is by no means uncommon to find in the *post-mortem* room that there are urates in the joints of persons who are not known to have had manifest gout, and that such urate deposits are often associated with granular kidneys, hypertrophied heart, degenerate vessels, and cerebral hæmorrhage, I think that many people who have the forms of headache and the history above described, and are easily affected by butcher's meat, and, indeed, resemble cases of Bright's disease in the manifest benefit they often derive from leaving it off altogether—I think that many of these cases tend to degenerate in this direction as years go on, and perhaps finally to enter the *post-mortem* room under some or all of the conditions above mentioned. So that I am inclined to believe that the diet treatment of these forms of headache may mean much more than the alleviation of their pain, and that if it is fortunately begun early in life, it may possibly be the means of preventing, or greatly delaying, the more serious and fatal developments."

I believe now more strongly just what I was beginning to see then, that from the uric acid headache to chronic Bright's disease the only change is one of degree.

I have now seen quite a large number of cases in which periodical sufferers from the uric acid headache have come to suffer from albuminuria and chronic Bright's disease; and I frequently have under my care cases, of which I shall give some notes, and in which the transition from migraine to morbus Brightii is occurring before our eyes.

The alteration in my diet has not only prevented my having a headache more than two or three times in a year (in place of forty to fifty times), but it has rendered the attacks in every respect less severe; the coldness of the skin and extremities is less, the pulse

is almost never as slow or of as high tension as it used to be; so that a rate below 60, or tension as high as that in fig. 44, is quite rare, and my general level of blood pressure has been lowered to a corresponding extent. Thus the circulation and metabolism in my skin and other important organs have not been hindered to anything like the extent they would have been had I continued my meat diet during these years, and I have so far escaped albuminuria and Bright's disease.

I believe it is by no means rare for sufferers from the uric acid headache to have a little albuminuria at the time of the attack or just before it is over, and some have albuminuria with their bad attacks but not with their slight ones. My experience in this respect is by no means singular, as I notice an article by Dr. Stewart Lockie, in the *British Medical Journal*, 1886, vol. i., p. 1059, on the albuminuria of adolescence and headache as its chief symptom. He also mentions the frequent presence of a gouty family history in these cases.

The analogy between cyclic albuminuria and migraine is also pointed out in a paper abstracted in the Epitome of the *British Medical Journal*, June 6, 1896, p. 89.

Again it will have been gathered from what I said of paroxysmal hæmoglobinuria in chapter xii., that I look upon it simply as a paroxysmal fluctuation in urate excretion, entailing the passage of an excess of uric acid through the blood. It is, in fact, a severe uric acid storm, and the headache in this case, just as in the cases of albuminuria mentioned above, is frequently present.

I believe there are to be met with all gradations, from the blood changes of anæmia produced by uric acid to the hetero-albuminæmia (Semmola) and albuminuria, and finally to the hæmoglobinæmia and hæmoglobinuria of the paroxysmal disease, the factor immediately underlying these blood changes being a deficient circulation in the skin and other important organs of metabolism, and behind this again, and the cause of subsequent changes, is an excess of uric acid in the blood.

The obstructed capillaries, which raise, on the one hand, the pressure in the arterial system, diminish, on the other hand, the circulation through the organs and tissues of the body; headache, mental depression and fits represent, probably, the effects of the high blood pressure on the intracranial circulation, while arterial degeneration and hypertrophy of the heart are some of its effects on the vascular system; on the other hand, the cold skin and extremities, certain alterations in the skin and other structures up to

Raynaud's disease, the atrophied skin of Bright's disease, and certain changes in the blood and circulating albumens, ranging from anæmia to hetero-albuminæmia and hæmoglobinæmia (these being accompanied by diminished formation of urea just as we have seen it alling in fatigue [figs. 46 and 47], and indeed wherever, even in physiological conditions, there is an excess of uric acid in the blood), represent the effects of the defective circulation on the great metabolic tissues, where the combustion of the body is carried on.

In so far as these changes are due to uric acid, they are at first functional and may be completely recovered from, but when the uric acid storm is severe, and repeated every week for years, the interference with circulation is sufficiently great and prolonged to produce atrophy and degeneration of tissues, and then the full picture of Bright's disease gradually unfolds itself and complete recovery is no longer possible.

The only course now is to reduce the metabolic needs of the body within the limits which atrophied structures may suffice to perform, just as occurs sometimes in phthisis, when a patient may last for years with only a lung and a half, or less, because the respiratory needs of the body have been correspondingly reduced.

In saying this, it must not be lost sight of that external conditions, such as temperature, will very greatly influence in one way or another the effects of uric acid on the skin circulation; while an internal condition, such as dyspepsia, by keeping up for weeks and months a more or less severe collæmia (see chapter x.), may bring into existence, in a comparatively short time, its worst effects on metabolism and nutrition. My clinical observation leads me to believe that chronic Bright's disease not very rarely takes origin in this way from chronic dyspepsia.

See also a paper by Dr. Tirard in the *Lancet*, 1896, vol. ii., p. 377, on dyspepsia as a predisposing cause of morbus Brightii; but it is far more than a predisposing cause; it is one link in a chain of causation and itself also a result of collæmia, which it helps to continue and intensify.

The best proof that uric acid exerts the effect on the vessels which this pathology postulates is, I think, to be found in the fact (previously gone into, chapters ii. and iii.) that the urinary water varies from hour to hour, and day to day, inversely as the uric acid excreted along with it, and the further fact that very numerous drugs which diminish the uric acid increase the water, while others which increase the uric acid diminish the water.

Add to this that excess of uric acid in the blood diminishes the

formation of urea both in physiology and pathology, and determines the onset of fatigue (chapter viii., figs. 46—49), and we have some pretty convincing proofs of its great and far-reaching powers over the metabolism and combustion of the body.

The administration of urea in the treatment of tuberculosis is an interesting instance of the law that anything that clears the blood of uric acid acts as a stimulant to nutrition and metabolism (see p. 123). It has been pointed out that the urea taken is not excreted as urea, but is broken up and metabolised in the body, and as far as I can see this is true, for though when I, while fasting in the morning, took urea, there followed an immediate rise in the excretion, I think that this was merely due to stimulation, as there was a corresponding rise of acidity, and that here, just as with sugar and acetic acids in figs. 4 and 5 of "Diet and Food," the rise of urea was a result of stimulation and not a mere excretion of the urea swallowed; hence urea is a stimulant of nutrition and combustion because it clears the blood of uric acid.

As some appear to have misunderstood the bearing of my remarks on the circulation of the kidney (Sewell, *Medical News*, Philadelphia, September 16, 1893), I may restate them here.

It is no doubt quite true, as this observer points out, that physiological experiment has shown that the blood supply of the kidney varies directly with blood pressure; but in these experiments the capillaries of the kidney remained neutral, whereas my point is that in collæmia the capillaries of the kidney are not neutral, but, like the vessels of the skin, the eyes, and the salivary glands, they are more or less decidedly obstructed; and what I suggested was that this obstruction overcame the power of arterial blood pressure to force blood through the kidneys, and the remarks I have quoted from Sir T. Lauder Brunton (see fig. 33) show that this is his opinion.

Clinically I think we meet with scanty urine under two conditions: (1) when, the heart being normal, the obstruction of capillaries is abnormally great, and the kidney circulation is consequently defective; (2) when the obstruction of capillaries is not above normal, but the heart is weak or diseased, and has not the power to drive the blood through them.

The failure of circulation is, in both cases, due to the fact that the heart has not power to do what is required of it; but a finger on the pulse will enable us to distinguish between them, for in the first case there will be high blood pressure, in the second almost none; the same argument applies to the circulation in all the tissues of the body, and I have already alluded to it in connection with the incidence of Raynaud's disease in girls and women.

This also explains the absence of dropsy in chronic Bright's disease, for in this the heart at first hypertrophies and works up to its troubles, but later on its nutrition, with that of the whole body, suffers severely, it fails and dilates, and then retention of water and dropsy supervene because the capillaries in the kidney and elsewhere get the best of it.

When anything, *e.g.*, previous pericarditis, prevents the heart from undergoing this conservative hypertrophy, the primary dropsy is marked and persistent, and the end is so rapid that there is no time for chronic changes in the kidney to take place.

Having thus given an outline of the position I have been led to take with regard to the causation of albuminuria and Bright's disease, I shall now give more in detail some of the facts on which it is founded.

In a paper on "The Connecting Link between the High Tension Pulse and Albuminuria" (*British Medical Journal*, 1890, vol. i., p. 65), I mentioned certain points which seemed to me of interest in connection with the writings of the late Dr. Mahomed and the late Professor Semmola as bearing upon the causation of the disease, and suggested that hetero-albuminæmia, of which the latter writes, and to which the kidney lesions found *post mortem* are secondary, gave us a good explanation of the causation both of Bright's disease and of so-called functional albuminuria.

I will now mention a few of the points in this paper.

Dr. Mahomed pointed out that, though a high tension pulse is a common and characteristic feature of Bright's disease, it might nevertheless be present for several years before there is any albuminuria. He said that the high tension and other signs of what he called the pre-albuminuric stage of Bright's disease were probably due to a poison in the blood, and I suggested that many of the signs and symptoms he spoke of were those of collæmia, and that the poison he was in search of was probably uric acid.

Dr. Mahomed also showed that in certain cases of temporary albuminuria, about which I shall speak at greater length presently, the appearance of the albumin was preceded and accompanied by an increase of arterial tension.

I then quoted at length from the works of Professor Semmola, who shows that the appearance of albumin in the urine is due to the presence of an excess of diffusible albumin in the blood (hetero-albuminæmia), the kidney lesions found after death being due to the irritation which this foreign albumin eventually sets up in passing through its glomeruli and tubules.

I pointed out in support of Semmola's thesis that Stokvis, in one of his experiments with egg albumen, did produce some kidney irritation, resulting in the passage of serum albumin into the urine.

That, taking Bright's disease as a primary alteration (inflammation) of kidney structure causing serum albuminuria, there is nothing to account for the excess of diffusible albuminoids in the blood, as to the existence of which in nephritis the observations of Semmola do not stand alone.

I further said that, while the theory of primary kidney lesion quite failed to account for the clinical symptoms of cases of so-called "functional" albuminuria, the theory of primary blood lesion (hetero-albuminæmia) might account for them completely.

The chief arguments of Professor Semmola are as follows, and I take them from the work of Dr. Labadie-Lagrave (*Urologie clinique et Maladies des Reins*, Paris, 1888, p. 714, *et seq.*):—

(1) The amount of albumin in the urine varies with the amount of albumen in the food, and not with the renal lesion; therefore the albuminuria is not due to the renal lesion.

(2) The cause of Bright's disease is the action of cold and damp on the skin, but this cold or damp in chronic cases is not able of itself to determine hyperæmia of the kidney; that is to say, the lesion eventually found in the kidney is not the direct result of the action of cold and damp on the skin, therefore there must be some intermediary.

(3) This intermediary is unassimilable albumen, certain portions of the circulating albumens being rendered unassimilable and diffusible by failure in the metabolism of the skin.

(4) This unassimilable albumen is eliminated by the kidneys and other organs, and gradually produces irritation and parenchymatous and interstitial changes in their structure—Bright's disease.

Thus Labadie-Lagrave says (previous reference, p. 719): "Ainsi donc: accumulation dans le sang d'albuminoïdes inassimilables: premier fait, et consécutivement lésions rénales. Tel serait, d'après Semmola, l'enchainement du processus dans le mal de Bright."

He then points out that as a result of this doctrine there must be from the outset a diminution of urea; and that Semmola has long pointed out this diminution, and the fact that it is due to diminished formation, as the amount of urea in the blood in early Bright's disease is less than in healthy blood, so that there is no accumulation, nor is there any increase of kreatine, kreatinine, or other intermediate nitrogenous products.

I have also pointed out in chapter iv. the way in which collæmia,

by interfering with the circulation in the liver, muscles, skin, &c., may hinder metabolism and lessen the formation of urea, and the further fact that the formation of urea, as well as the symptoms of fatigue, can be controlled by controlling collæmia; here, indeed, we have in fatigue an epitome of Bright's disease; prolong the collæmia over weeks and months and we have to deal with actual Bright's disease, which again, so long as it is recent, can also be controlled in exactly the same way that fatigue can be, and with the same drugs, or even the same metal (mercury).

But this theory of hetero-albuminæmia is no mere hypothesis, for Semmola bleeds his patients and demonstrates that their blood contains excess of albumins that diffuse; also that blood which contains this excess will produce albuminuria when injected into a dog, and this albuminuria will be proportional to the amount of diffusible albumin in the blood injected.

Labadie-Lagrave (previous reference, p. 727) further points out that Semmola has shown that in Bright's disease there is not only anæmia of the skin, but that its glands, epithelium and cells of the Malpighian layers have undergone extensive atrophy, this doubtless carrying with it great interference with function and healthy metabolism; while in albuminuria due to other causes, as morbus cordis, alcoholism, gout, there is no alteration whatever in the structure of the skin, and he concludes his notice as follows: "Telles sont les dernières recherches toutes récentes du professeur Semmola, qui viennent si brillamment à l'appui de la théorie dont il est l'ardent défenseur" (p. 728).

On this theory an albuminuria is on all fours with a glycosuria. No alteration of kidney structure has been suggested to account for the latter. On the contrary, it is known that any excess of sugar in the blood at once passes off by the kidney, and that this sometimes causes hyperæmia and irritation of the kidney. On Semmola's theory albuminuria is due to excess of diffusible albumin in the blood, and this, in its passage through the kidney, causes irritation and nephritis.

Lastly, I pointed out that uric acid (the poison of which Mahomed noted the effects, and which I identified from the clinical symptoms it produced) might bring about hetero-albuminæmia, with secondary albuminuria and nephritis, and thus form the connecting link between the high tension pulse, &c., of the pre-albuminuric stage, as observed by Mahomed, and actual Bright's disease.

I suggested that uric acid, by obstructing the capillaries (as it

does when it raises the tension), might interfere seriously with the metabolism of albuminoids both in the liver and the skin (which accords with Semmola's facts as to the causation of hetero-albuminæmia), and that when this action is very intense we might get breaking up of hæmoglobin itself, as in paroxysmal hæmoglobinuria (the most intense condition of hetero-albuminæmia), the symptoms accompanying which I pointed out are just those of a uric acid storm (collæmia).

On the other hand, I pointed out that the violent action of uric acid on the capillaries might account for that disease which is most nearly related to paroxysmal hæmoglobinuria, and, like it, is accompanied by marked clinical signs of collæmia, namely, Raynaud's disease; and that the symptoms of the pre-albuminuric stage, according to Mahomed, are cold hands and feet, imperfect digestion, bronchitis, gastric catarrh, headache (especially hemicranial), loss of memory, depression, weariness, cloudiness of intellect and hypochondriasis, and after what I have said in previous chapters as to the causation of these symptoms by uric acid I must leave my readers to judge of their meaning.

We can now also see, in reference to Semmola's facts as to the effects of cold and damp on the skin, that these may not only, as he supposed, directly contract the vessels of this important tissue, but, by precipitating a collæmia, just as in the test-tube (see chapter v.), may still further hamper the circulation, nutrition and metabolism, especially in those who have on the one hand much uric acid available in the body, and on the other a heart which (as so often happens in pregnancy, for instance) is weak relatively to the increased work required of it.

It seems, then, that at this point we have three chief theories as to the causation of albuminuria:—

(1) That it is due to heart failure (which applies, I suppose, only to temporary albuminuria, and not to Bright's disease), though no doubt heart failure may greatly intensify the evil effects of collæmia on nutrition and combustion, as I shall have to point out further on.

(2) That it is due to irritation of the kidney by a poison in the blood (Mahomed).

(3) That it is due to hetero-albuminæmia, just as glycosuria is due to glycæmia, and that irritation and structural change in the kidney are secondary (Semmola).

And to this last I have added the suggestion that, while hetero-albuminæmia may be due to the action of cold on the skin, the obstruction of vessels which uric acid produces may bring about

very similar effects, or greatly increase the power of cold; and cold, as we now know, does in its turn act as a precipitant of uric acid.

Then in the *Guy's Hospital Reports* of 1881 we find Dr. Mahomed speaking of cases of nephritis, and also of convalescence from scarlatina, in which there is no albumin while they are in bed, but it occurs on getting up and going out; and with reference to this he says (p. 416): "The rapidity of the change is too great for the kidney condition, determining it to be a structural one; it must be functional, or more probably a vascular phenomenon. The fact stands, therefore, that the same kidney, and that a diseased one, can produce alike normal and albuminous urine." This observation, it will be noted, is in complete accord with that of Semmola quoted above, that the albuminuria does not correspond with the kidney lesion.

I do not deny that certain vascular conditions can produce albuminuria (notably congestion in severe morbus cordis), but I do deny that cardiac weakness and congestion account for the albuminuria in the cases of so-called functional albuminuria (mentioned in my paper in the *British Medical Journal*, January, 1890, p. 65) or for temporary albuminuria in cases of chronic Bright's disease, such as those spoken of by Dr. Mahomed.

I also deny that uric acid in the blood directly irritates the kidney and produces albuminuria and eventually nephritis, though I have no doubt that an accumulation of urates, or for that matter of pigment or other matters in the kidney, or even the mere passage through it of sugar, bile, cantharides, &c., may produce congestion and slight albuminuria, but that is in many ways a different matter from nephritis. Urates also may accumulate to a large extent in the kidney just as they do in the joints and other fibrous tissues—"gouty kidney"—but this also is a different thing from parenchymatous and interstitial nephritis.

As to heart failure, this may produce congestion of the kidney and albuminuria. Semmola himself admits it, but he points out that when albuminuria is due to this cause the blood does not contain any excess of diffusible albumin, which at once distinguishes cardiac cases from those of Bright's disease; and cardiac kidneys are generally easily differentiated from those of Bright's disease *post mortem*.

In transitory albuminurias in apparently healthy subjects not due to mechanical causes, in albuminuria in the course of *maladies dyscrasiques*, and in the albuminuria of convalescence from scarlet fever, Semmola finds excess of diffusible albumin in the blood—an

excess which is proportional to the amount of albumin that is eliminated in the urine.

Mahomed's theory regarding the local irritation in the kidney produced by his hypothetical poison as the cause of albuminuria and Bright's disease, fails to explain two points of great importance in that disease: (1) Semmola's excess of diffusible albumin in the blood, and (2) the diminished output of urea which is generally acknowledged to accompany or even precede the onset of Bright's disease.

As Semmola remarks, his hetero-albuminæmia gives the best possible explanation of the diminished urea, for if albumen is not metabolised, but excreted unaltered, the formation of urea must obviously be reduced.

I would also remind my readers again that in all collæmia there is a diminished formation and excretion of urea, and that from my point of view chronic collæmia is equivalent to the pre-albuminuric stage of Mahomed, and leads inevitably to chronic Bright's disease, so that I can easily account for the diminished urea.

But if these theories fail, let us see how far the theory of hetero-albuminæmia will carry us in explaining the history and symptoms of Bright's disease.

Semmola says that anything that interferes with the functions of the liver or the skin may hinder the proper metabolism of albumens and produce hetero-albuminæmia, which he regards as the first stage in the causation of albuminuria and nephritis.

I have suggested that uric acid, by its action on the capillaries, may interfere in the way sketched out above with the functions of the liver, and by obstructing its capillaries, as it clearly does during an attack of uric acid headache, may seriously interfere with the functions of the skin; hence, in accordance with Semmola's reasoning, it may produce hetero-albuminæmia and albuminuria (see also chapters iv. and v.).

No taker of meat and tea ever has as quick a capillary circulation in the skin as he who abstains from these poisons; hence all takers of these are visibly moving in the direction of Bright's disease.

I pointed out in my paper on albuminuria (previous reference) that the theory of heart failure would not explain the cases described by Dr. Dukes (*British Medical Journal*, 1889, vol. i.), in which, in association with high tension pulse, there was albuminuria when the patients were up and about, except when they were on milk diet, but no albuminuria when they were in bed, no matter what diet they were given. These cases differ from those of Mahomed previously

mentioned, in that another factor in causation (namely, diet) is introduced. Mahomed's cases might have been due to heart failure, because the albumin appeared when they were up and about and disappeared when they were in bed; but in Dr. Dukes's cases the patients might be up and about, and yet have no albuminuria so long as they kept to milk diet. It appears to me to be nonsense to say that the heart failed on ordinary diet, but did not fail on milk. Again, we know that in these cases there was no primary failure of the heart, for the blood pressure was above normal. Hetero-albuminæmia, however, will explain these cases easily, for milk is, according to Semmola, the form of albumen which requires least elaboration by the skin, and I have suggested that this is due to the fact that it is really the product of a skin gland; but the meat of ordinary diet introduces some uric acid, which will increase the collæmia in the blood. Again, they have no albuminuria while in bed, no matter what diet is taken, because the warmth of the blankets counteracts the effects of uric acid, by preventing the precipitation of colloid uric acid.

I have also spoken of the albuminuria that sometimes follows a cold bath, and have suggested that it is due to hetero-albuminæmia following the contraction of the vessels of the skin by cold, more or less aided by uric acid, which is generally in excess in the urine and blood in the morning hours; heart failure, again, seems to me an inadequate explanation, as the heart has just had the benefit of a night's rest and recuperation.

Again, in Dr. Dukes's cases the albumin is excreted in greater quantity after meals, especially after breakfast, than at other times of the day. Why should the heart fail in the morning after breakfast more than at any other time?

In a more recent paper (*Lancet*, 1891, vol. ii., p. 1327) Dr. Dukes attributes the albuminuria of adolescence, and the Bright's disease into which he thinks it may eventually develop, to more or less chronic congestion of the kidney; but, as before remarked, a congestion of the kidney will not explain an excess of diffusible albumin in the blood or a diminished formation of urea.

My explanation of Dr. Dukes's cases is collæmia producing obstructed vessels and high blood pressure, hampering the functions of the liver or skin, or both, producing hetero-albuminæmia and albuminuria; and the albuminuria is most marked at those hours at which, in the natural physiological cycle, the collæmia is most intense, the pulse slowest, and the urinary water lowest (see figs. 2 and 3). Dr. Saundby points out ("Lectures on

Bright's Disease," p. 15) that in Bright's disease also the albuminuria is greatest after meals, and especially after breakfast, and where I have been able to examine the point this has certainly been the case; so that these "functional" cases resemble, in this respect at least, the organic disease, and I for one am quite ready to believe that they may pass into it.

On the other hand, a mechanical albuminuria, or one due to actual lesion of kidney structure, does not show this increase after breakfast.

It is interesting to note that a precisely similar relation to morning hours is found in glycosuria and diabetes, and no doubt from the same cause; and, as we shall see in the next chapter, an allowance of bread, which if taken at breakfast will cause or increase glycosuria, will, if taken later in the day, produce no such effect.

Dr. Dukes considers that this albuminuria of boys is dependent on some condition of the vasomotor system, but he overlooks the fact, or at least gives no explanation of it, that the vasomotor system is quite happy in any position, vertical or horizontal, so long as the boys only take milk.

Again, he tells us that these boys very often faint or feel faint in the morning hours, and that this is so common a symptom of albuminuria that it at once leads him to examine the urine; but surely after what has now been said on the circulation in previous chapters we want nothing more to tell us that these boys have high blood pressure, that their high blood pressure is due to collæmia, and that it is highest in the morning hours because the collæmia is then greatest (see figs. 38—43).

And every word that I have said in previous chapters on the effects of collæmia on circulation, nutrition, and combustion, on anæmia, hæmoglobinæmia, hetero-albuminæmia, and shall have to say of glycæmia, applies to those cases of albuminuria of boys, and explains completely every fact with regard to their causation.

They are boys of the upper classes unwisely fed on a great excess of animal flesh; they are coming to the end of their period of most active growth (sixteen) and are getting some collæmia, just as their sisters do a year or two earlier, and the intensity of this collæmia will be proportional to the amount of meat they have eaten, and the greatness of their falling off in developmental activity; and any febrile disease coming at this time and followed by post-febrile collæmia may precipitate this condition.

The collæmia causes slow capillary reflux and high blood pressure, and this may cause more or less heart failure or fainting

in the morning; but collæmia with heart failure means, as we have already seen in the case of Raynaud's disease, combustion which is very defective indeed.

This defective combustion is completely upset by the albumens of meat, but is still equal to the combustion of the albumens of milk; the meat albumens, however, produce hetero-albuminæmia and albuminuria, and, if the real cause is not detected and treated, may lead on to Bright's disease.

Practically, all conditions in which the capillary reflux is slow and the blood pressure more or less high in consequence are conditions of defective combustion, and this defective combustion will be greatly increased by heart failure if it occurs.

I most strongly advise those whose children suffer from any such troubles, and have well-marked slowing of the capillary reflux, to waste no time in clearing the blood of the poison which prevents its circulation. Uric acid can be diminished, and if this relieves and cures we may conclude that the vasomotor nerves or other organic factors were unimportant.

Some talk of functional albuminuria and define it as albuminuria in the apparently healthy. It appears to me that, apart from irritation by urates or oxalates, albuminuria in the apparently healthy is quite rare. I scarcely remember to have seen a single case in which there were not well-marked signs of defective circulation, such as slow capillary reflux, high blood pressure, and some alteration of the sounds of the heart. In most cases also there is more or less anæmia and a history of headache, vertigo, or depression.

I see plenty of albuminuria in schoolboys and undergraduates, but always accompanied by signs of collæmia, and often by those of heart failure as well. In some cases the collæmia accounts for nearly everything, in others the weak heart is the larger factor. In the former case a change to a correct diet suffices to cure, but in the latter you may quite fail unless you get the heart strong, and this it is not always possible to do; so that in the albuminuria of adolescents, just as in the full picture of Bright's disease, the presence of weakness of the heart or morbus cordis makes the prognosis less hopeful.

Now let us look at the etiology of acute Bright's disease. The late Sir W. Roberts says ("Urinary and Renal Diseases," 4th Ed., p. 471): "That complex of impressions which is familiarly known as taking cold is the common cause of Bright's disease in its acute form"; and in common with other writers he mentions also scarlatina and alcohol.

After what I have said in previous chapters it is unnecessary again to point out the way in which all these factors act in producing a fluctuation in the excretion of uric acid, the fluctuation resulting in the production of more or less severe collæmia, which brings about, we are supposing, hetero-albuminæmia, albuminuria, and nephritis.

I do not deny that high blood pressure and obstructed capillaries, which interfere with the circulation in the kidney and produce scanty urine, do probably, to some extent, also interfere with its nutrition, and that where such high pressure is frequently present the interference with nutrition may be carried to the extent of producing structural change; but granting all this we are no nearer to the explanation of Semmola's facts—the excess of diffusible albumin in the blood and the diminished formation of urea in Bright's disease.

It has over and over again been pointed out that we have to deal with diminished formation, not with diminished excretion of urea; now a primary kidney lesion cannot possibly account for deficient formation, though defective combustion accounts for it completely, and defective combustion is seen in miniature almost every day in physiology, and fig. 3 shows, I think, that the rise of urea that follows breakfast is less rapid and marked than that which follows lunch, not because lunch is a better meal than breakfast, but because metabolism and combustion are held down throughout the morning by the collæmia represented in the large excretion of uric acid in the same figure. Hence, of course, there is an increase of albuminuria in these same morning hours.

And it is possible by administering to a patient a test meal and watching the hourly excretion of urea that follows, as is done in physiological conditions in the figures of my book on "Diet and Food," to gauge with considerable accuracy the activity of metabolism and combustion in that patient's body.

Then we shall also see in the cases that follow that albumin diminishes and urea rises in pretty definite and precise relation to the quickening of the capillary reflux and the reduction of blood pressure, and I shall be interested to see how those who hold to the theory of kidney lesion can explain these facts. Let them tell us, if they can, why iodides and mercury will cure a kidney lesion, while citrate of potash makes it worse; why 2 oz. of bread cause glycosuria at breakfast while 4 oz. do not at dinner.

In the *Wien. klin. Rund.*, January, 1895, the late Professor Semmola again puts forward some of the main points of his

important researches, such as the fact that the subcutaneous injection of egg albumen in dogs causes albuminuria, which is not at first attended by any histological changes in the kidney, and draws the conclusion that egg albumen can pass through the kidney without there being any lesion of its epithelium. But continue the passage of albumen through the kidney for more than forty-eight hours and hyperæmia and progressing chronic nephritis ensue.

Here we have produced experimentally exactly what we see occurring almost daily before our eyes in Nature; thus a man may have migraine every week for a long time and the passing of a little albumin for a few hours at the worst part of the attack may produce no change in his kidney whatever; but if his collæmia becomes more chronic, and if the albuminuria is continued from day to day or even week to week, the result is different. The patient perhaps tells you that during the last month or two his headaches have been more frequent and severe, and you examine his urine and find distinct evidence of kidney lesion.

In these two months the change has been made from functional to organic, from migraine with temporary albuminuria to Bright's disease with chronic albuminuria, and though we can still control the uric acid and the hetero-albuminæmia and functional albuminuria, the high blood pressure and the headaches it produces, we cannot put back the damaged kidney structure or prevent the passage of serum albumen through its injured tissues, or reinstate in their original integrity the skin, muscles, liver, &c., the great metabolic tissues, which are similarly damaged.

So far as they are functional, true pathology gives us power to control these cases, and even the kidney lesions tend to repair themselves if the cause of irritation is removed before the damage is too great.

Combustion here again explains what a mere local kidney lesion theory cannot, namely, why the result continues after the cause has ceased to act, why the acute disease passes on into chronic when the cold, wetting, or other cause which originated the acute disease has passed away.

But a fire that has been nearly put out by water will burn low for a long time after the water has dried up, and so will the human fire that collæmia has nearly extinguished, especially when, owing to large collections of urate in the body, the collæmia can be kept in constant operation for months and months.

Semmola also points out that the amount of albumin eventually excreted in these experimental injections corresponds in no

way with the amount of albumen injected, nor yet with the extent of the kidney lesion, but rather with a change in the composition of the blood itself, which makes the serum albumen morbidly diffusible; in other words, the continued injection into the skin of an abnormal albumen eventually brings about such changes in metabolism and nutrition that the blood serum itself becomes imperfectly elaborated or metabolised, and in consequence abnormally diffusible.

In any case the quantity of albumin excreted in Bright's disease depends on these blood conditions, and not at all on the extent of the kidney lesion, just as in paroxysmal hæmoglobinuria we get an enormous quantity of albumin with blood changes, but no kidney changes in proportion to it.

On the other hand, in the case of direct kidney lesions, such as those produced by cantharides, the amount of albumin is small compared with the kidney lesion.

Semmola says that continued injection of egg albumen eventually produces albuminuric retinitis, and that true Bright's disease can be artificially produced in this way (from my point of view this would be equivalent to putting out the fire by too much coal); also that in acute infectious diseases, toxic, rheumatic and gouty dyscrasies, the albuminuria is due to modifications in the diffusibility of the albumin of the blood.

The facts with regard to the presence of these diffusible albumins in the blood of Bright's disease, or, at least, in certain stages of Bright's disease, seem to be confirmed by the researches of Freund, and have been accepted by Vulpian, Labadie-Lagrave, and others I have quoted. But I shall have more to say on these points when I come to deal with cases.

Now, cold raises acidity, fever raises acidity, most alcoholic drinks raise the acidity, and these last, acting over long years, retain in the body large quantities of urate, which provide the material for eventual chronic and severe collæmia in old age or other failure of nutrition; and this collæmia is to my mind the cause of the chronic nephritis so often found in the *post-mortem* room with chronic gout (see Dr. Norman Moore, *St. Bartholomew's Hospital Reports*, vol. xxiii., p. 289). Further, the excess of urates which under these conditions passes into the blood and out in the urine is the cause of the gravel and calculus so frequently met with in the declining years of life (compare also case mentioned on p. 49).

But where the collæmia is more sudden and severe, *e.g.*, when it results from sudden severe chill (a case under my care got his

disease by being called from the stoke-hold of a steamer to stand twelve hours or more on deck, where he got wet through in five minutes and had to remain so), it may produce not only hetero-albuminæmia, but the urate may, as I have suggested, acting in sequence to the chill, attack also the red cells and cause hæmoglobinæmia and hæmoglobinuria, and it appears that in some cases paroxysmal hæmoglobinuria has formed the starting point of acute Bright's disease (*Lancet*, 1889, vol. ii., p. 1007).

With regard to the causation of paroxysmal hæmoglobinuria, the late Sir W. Roberts says (*loc. cit.*, p. 162): "Most observers are now agreed that the solution of hæmoglobin in the serum precedes its appearance in the urine, and that the symptoms of kidney affection which are sometimes present are due to the irritation produced by the passage of the hæmoglobin through these organs."

Here, then, in the case of paroxysmal hæmoglobinuria the whole of Semmola's contention is quietly admitted; first of all that the escape of the blood constituents in the urine is due to their breaking up in the circulation itself, and second, that their passage through the kidney causes irritation in that organ.

If it is granted that in place of such violent and temporary destruction of blood elements we may have severe hetero-albuminæmia lasting continuously over several days (less intense, but of longer duration), may we not see in this the causation of acute Bright's disease as it is met with clinically? And there is no difficulty in granting this, as numerous observers (notably Dr. Stephen Mackenzie, *Lancet*, 1884, vol. i., p. 243) have seen albuminuria both preceding and following the hæmoglobinuria.

Further, the albuminurias which accompany migraine, epilepsy, or convalescence from acute disease, all conditions in which there is often the most obvious and severe collæmia, and of which paroxysmal hæmoglobinuria is a mere exaggeration, almost of themselves suffice to demonstrate that the association of albuminuria with collæmia is no accident; and when we consider that even in physiology uric acid controls the formation of urea, we can at once understand the fall of urea as seen in the above functional troubles as well as that which is so marked a feature of the onset of Bright's disease.

In Bright's disease we shall also see that when we clear the blood of uric acid and allow combustion to go on freely, the albumin diminishes in proportion as the urea increases, so that there is no room for doubt as to the relation between these two substances.

The following case throws, I think, some light on the causation of albuminuria in the way I am suggesting, by the action of cold or uric acid or both on the vessels of the great metabolic tissues:—

E. H., aged 44, a patient of Dr. Tomson, of Luton, Beds, to whom I am indebted for the history of the attacks.

Complains of attacks of "liver" every three months or oftener, accompanied by extreme mental depression, shivering and retching, followed by a rise of temperature. Subject to these attacks as long as he can remember.

Had fits at 5 and 12 years of age.

His mother died of phthisis at the age of 50.

His father is still alive and well, age 83.

Two brothers (one an imbecile) and one sister died of phthisis.

One sister has functional twitching and contractions of the muscles of both arms.

Other members of the family exhibit evidences of an insane neurosis.

Patient was operated on for anal fistula in 1892.

The following is Dr. Tomson's account of an attack he saw in December, 1892:—

"Condition distinctly hysterical; throws himself about on the couch, and repeatedly cries out 'Oh, I'm so bad! Oh, I'm so bad!' A constant restlessness. He shivers, and the teeth chatter; occasional retching, but nothing brought up; pulse 108; artery contracted, high tension, temperature just under 100° F., liver much enlarged, three fingers' breadth below the ribs. Urine high coloured; no albumin.

"In this condition he remains for two or three days and then gets better. The more noticeable features are the rapid enlargement of the liver, and its equally rapid subsidence at the termination of the seizure, and the intense misery of the patient. He has severe attacks like this about every three months, and less severe attacks between times."

When I saw him he told me that he had a headache on the previous day, which began at 11.30 a.m.

His pulse was only 54, and both to finger and sphygmograph showed extremely high tension; the first sound of the heart was prolonged or reduplicated between the apex beat and the sternum, and the second sound was loud; he had thus both the cardiac and arterial signs of high tension. The liver dulness was not enlarged, and its edge could not be felt; and now we come to a point of very great interest. The urine which he passed here (12 noon) was high coloured and specific gravity 1020, contained a large quantity of albumin, 4 per 1,000 (Esbach), and no sugar. Under the microscope it showed numerous oxalate crystals and a

few casts, hyaline and slightly granular. This was the first time albumin had been noticed in his urine.

Let us try to group these symptoms and estimate their meaning. *Obstructed capillaries and high blood pressure* are shown in the attack described by Dr. Tomson, in the condition of the pulse, the shivering and teeth chattering, the high coloured and probably scanty urine. The hysterical conditions on the one hand and the mental depression on the other are the effects of the alterations in the intracranial circulation, as I have already explained in chapter viii., just as the shivering may be the effect of the deficient circulation in the skin; I have myself had just such shivering or slight rigors in my attacks of uric acid headache when they used to be severe. All these conditions are temporary and periodic, and therefore probably not organic.

What is the meaning of the marked enlargement of the liver? I suggest that it is a venous congestion or hyperæmia due to failure of the heart in its effort to overcome the capillary obstruction; when I saw this patient there was very high blood pressure, but the pulse-rate was only 54; there was therefore no sign of heart failure, and with this there was no enlargement of the liver. But in the attack described by Dr. Tomson the pulse-rate was 108, and yet he says the tension was high. Such a pulse-rate with high blood pressure almost certainly means heart failure, and it is possible that the vessels of the lungs were greatly obstructed (see chapter ix.), and that this told specially on the right heart and the liver.

What was the cause of the high blood pressure? Excess of uric acid in the blood; the urine was highly coloured and probably scanty, and we know that the urinary water is inversely as the uric acid excreted along with it; therefore there was an excess of uric acid in the urine and probably also in the blood. I look upon these so-called "liver" attacks as uric acid storms almost if not quite identical with my attacks of uric acid headache; and in these attacks I have often noticed some distinct evidence of more or less temporary congestion of the liver, such as pain, weight, fulness, or a feeling of heat or tension in the right hypochondrium, and these sensations are at their worst when blood pressure is greatest.

Now we come to the trouble at the time I saw him; again the signs of obstructed capillaries and high blood pressure were most marked in the heart and arteries; there was a headache, doubtless the result of this tension on the previous day, and the urine contained a quantity of albumin, together with some casts and some oxalates. It was free from albumin a day or two before, and became again free from albumin a day or two later.

We have here almost completed the picture, not of paroxysmal hæmoglobinuria, but of the next thing to it, paroxysmal albuminuria.

Now the point on which the whole of this chapter hinges is the way in which this albuminuria was produced; let us look closely at the meaning of the accompanying symptoms.

A urine of high colour and specific gravity, and therefore almost undoubtedly containing some excess of uric acid. Again, we have seen in the previous chapter that oxalates may mean the simultaneous excretion of intestinal putrefactive products (sulphuretted hydrogen) with an excess of urates; so that here we have independent evidence that an excess of urates was excreted; but why was there intestinal putrefaction? Because the vessels of the intestines, like all vessels in the body, were obstructed by the very uric acid which was passing in excess in the urine. We know that the vessels were obstructed on the day before the albuminuria, because high blood pressure was the probable cause of the headache from which the patient told us that he suffered.

Here is very strong evidence of the presence of high blood pressure and obstructed capillaries, and evidence that these had been present for at least twenty-four hours before I saw the patient and found albuminuria. We have also evidence that these capillaries were obstructed owing to the presence of an excess of uric acid in the blood.

We have seen in previous chapters that excess of uric acid in the blood may not only account for the blood changes of anæmia, but also for those of paroxysmal hæmoglobinuria, and we know that albuminuria may precede and follow hæmoglobinuria, so that it is extremely probable that hæmoglobinæmia and hæmoglobinuria are but more advanced stages of hetero-albuminæmia and albuminuria.

I am suggesting that the chain of causation in the case of this albuminuria was as follows: a uric acid storm or fluctuation of excretion resulting in collæmia, general obstruction of capillaries, deficient circulation in the skin, liver, intestines, and other organs of metabolism; as a result of this, retrograde changes in the albumens of the blood and tissue fluids (hetero-albuminæmia of Semmola), which in some cases go on to hæmoglobinæmia, but in this case stopped short at hetero-albuminæmia and albuminuria.

Some may say, "You spoke of congestion of the liver just now; why may not a congestion of the kidneys similarly produced account for the albuminuria?"

First of all, at the time of this albuminuria there was no evidence

of congestion of the liver, and again, even if we grant that there was congestion of the kidneys, that would not account for all the conditions; suppose that instead of stopping short at albuminuria the attack had gone on to hæmoglobinuria, how could any congestion of the kidneys account for the destruction of a million red cells in the blood stream itself?

No doubt in congestion of the kidneys due to morbus cordis, for instance, one gets a trace, even a considerable cloud, of albumin, but not as much as in this case, 4 per 1,000.

No congestion of the kidneys can account either for hæmoglobinuria or the hetero-albuminæmia of Semmola; any such explanation therefore falls to the ground.

The relation of such a case to those of eclampsia, recorded in the *Lancet*, 1901, vol. ii., p. 1610, is too obvious to need further explanation; all these conditions are uric acid storms, in which in some cases the headache, in others the nervousness or depression, and in still others the albuminuria or hæmoglobinuria, are the most prominent symptoms, as in the most interesting cases previously referred to, recorded by Dr. Atlee, and in the case which he mentions as being under my care, fits occasionally replaced headache and nervousness.

Taking the view that this patient's troubles were of the nature of paroxysmal albuminuria, and due to recurrent uric acid storms, the obvious indication was to reduce the uric acid income and formation; I accordingly suggested a considerable reduction in the amount of meat and animal food, and I believe he went beyond my suggestions and changed the diet completely. In the first six months after this change of diet he had no attack of "liver," no albuminuria, and was in many other respects much better, and a later report said that he had not had an attack for more than a year.

Thus the treatment seems to have had the same effect that it had in myself—with the removal of the cause the effect disappeared. And this is another point on which I wish to lay special stress, namely, that when the diagnosis of uric acid disease has been well and properly made, treatment of the uric acid should without fail effect a cure. On the other hand, an intentional increase of the uric acid should equally without fail make the symptoms worse.

Further, it is a distinguishing mark of these metabolic albuminurias that they are greatly influenced by diet, that, as pointed out by Semmola and others, the amount of albumin excreted is to

a considerable extent proportional to the amount ingested, and that by reducing this amount and, further, by taking it in a form which is easily assimilated (milk, Semmola), these albuminurias, so long as they remain functional, can be greatly reduced or cured; and the experiences of Dr. Dukes quoted above confirm what I am saying.

The parallel between an albuminuria and a glycosuria is here again absolute; both in their early stages are functional, and in both during this stage the whole of the albumin or sugar can be removed. Later there is a residue in both cases which neither diet nor drugs will suffice to remove; in the interval some of the great metabolic tissues, being continually exposed to the results of defective circulation, have undergone atrophy and change of structure, and the furnaces of that human body will never again be capable of consuming quite as much sugar or albumen as before.

If, on the other hand, nothing is done and the patient continues to form and take in quantities of uric acid, not only will his attacks continue, but they will get more severe as he gets older; for the slackening metabolism which comes with age will favour the passage of a larger and larger excess of uric acid through the blood, and thus the metabolic albuminuria, which was at first paroxysmal and functional, will become organic owing to waste of the metabolic tissues; structural changes will take place in the kidney owing to the constant irritation of hetero-albuminæmia, and so we gradually pass from a mere uric acid storm to fully developed morbus Brightii, and I have seen, as I say, quite a number of cases in which periodical sufferers have found their attacks getting more frequent and severe, and have then on examination, for insurance or other cause, discovered both albumin and casts.

On the other hand, I have seen quite a number of cases of albuminuria, either temporary or intermittent, where diet treatment has almost at once removed the albuminuria and many of its concomitant symptoms, and the cure has appeared to be permanent.

In further illustration of some of these points, I will now give a few notes of a case of great interest, which I owe to the kindness of my friend, Dr. C. P. Handson, of New Cross, S.E. He says:—

"I am writing to tell you of a case in which your uric-acid-free diet was eminently successful, and only regret that, owing to having taken no notes, or made any estimation of the uric acid in the urine, my account will be very fragmentary.

"Augustus M., aged 13, has always been a delicate boy, and frequently absent from school with severe headaches. Has never had rheumatism. One of the mother's relatives has rheumatism.

Family history otherwise unimportant. Before November, 1901, he was much interested in a cantata in which he was to sing. After it was over he appeared to lose all interest in his school work, and suffered from constant headaches, pain in the left side, and increasing weakness. This, in spite of tonics, feeding up, &c. (much beef-tea and bovril), became steadily worse.

"I saw him for the first time on February 19, 1902. He was not markedly anæmic, but was emaciated, and there was great muscular wasting. Standing was impossible owing to vertigo. If left to himself he generally fell straight backwards. If led he could shuffle along slowly, and even be got up and down stairs. There was marked scoliosis (from muscular weakness). Headache was almost constant, as also a feeling of nausea, which on two occasions ended in actual vomiting. The vertigo persisted even while lying down. Knee-jerks exaggerated on both sides; plantar reflexes absent; other reflexes normal. Optic discs normal (this was afterwards confirmed by Dr. Gee). Urine loaded with urates, very acid; sp. gr. 1024; no albumin or sugar. Pain over præcordium and left hypochondrium almost constant, and sometimes intense enough to wake him up at night. The apex beat is diffuse and thumping; in normal position, the second sound ringing and accentuated. The capillary reflux is very slow. Nothing of note in any other organs. Has attacks in which he says he feels 'dreadful,' 'desperate,' and seems to lose control of himself; once he bit his mother's arm. There was no anæsthesia or hyperæsthesia. The muscles reacted sluggishly to faradism corresponding to considerable wasting.

"I at once omitted the beef-tea and bovril from his diet, but otherwise did not alter it, and gave him iron and strychnine internally and ordered a belladonna plaster to the heart. His condition, however, deteriorated, and on March 17, 1902, Dr. Gee saw him in consultation. He was puzzled to give a diagnosis, and said the only definite thing was the paralysis. He at first gave a bad prognosis; but wrote to me the next day to say that, on thinking the case over, he thought it might possibly be hysteria, and, if so, that the boy would recover. He ordered a tonic containing liq. strychn. and liq. arsenici hydrochlor., which was taken until April 30, when, as there was no improvement, I substituted mist. acid. nitrohydrochlor. dil. before meals, and sodii sal. after meals, ter., and ordered a uric-acid-free diet.

"For a time his condition deteriorated still further [collæmia from change of diet]. On May 14 I changed the medicine to ferri et ammon. cit. On May 28 the urine was alkaline, sp. gr. 1028,

contained phosphates, but no albumin or sugar. The signs of high blood pressure were very marked, and the pain over the heart was said to be worse. On May 31 he was taking hyd. c. cret. gr. ii., bis, the iron being omitted. On June 4 I gave him a mixture containing sodii bromid., pot. iod. and tr. strophanthi in addition to the hyd. c. cret. He then very slowly improved. On July 12 he could walk a little about the room by making sudden rushes. If he walked slowly his gait was somewhat like that of a drunken man, and unless someone was at hand he would fall. I then went for my holiday. While I was away he took the pills (hyd. c. cret.), but no medicine, and continued with the diet. When I saw him again on August 5 the improvement was very marked. He could walk about by himself, though he had occasionally attacks of vertigo and swayed. The pain over the heart appeared only intermittently. I saw him again the other day, when he walked up to my house—a distance of about three-quarters of a mile. He is practically as well as ever he was, takes walks by himself, though he prefers a companion owing to occasional vertigo, and is fairly reconciled to his diet. His mother has, however, occasionally given him tea of late, of which course I have pointed out the folly.

"The signs of high blood pressure have not improved to an extent corresponding with the general symptoms, the capillary reflux at 8.30 p.m. being still ten to twelve half seconds. I believe if the diet is persisted in that the boy will become well and strong, but that otherwise there will be a relapse. He has grown several inches during his illness, and is beginning to gain flesh, though the scoliosis persists.

"In that case I at first sight thought the symptoms were probably due to chronic nephritis. When an examination negatived this, I went for cerebellar tumour. This was negatived by the absence of optic neuritis. His condition was so suggestive of some grave organic disease that it was not until Dr. Gee had failed to find any, and after his tonic had failed to effect improvement, that I felt justified in trying the effect of your diet. I certainly think that the end would have been death from some intercurrent disease at no distant date but for the stopping of all supplies of xanthins.

"It was the resemblance of his case to that described by you on p. 526 of 'Uric Acid'* that suggested the treatment to me, after organic disease began to appear improbable.

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* The case of E. H., given a little before; Dr. Handson's page reference is to the fifth edition.

In a later letter he adds:—

"Reverting to the case of Augustus M., as you say, it was most interesting that he got worse when first put on a uric-acid-free diet. Knowing, however, that according to your theory it was exactly what ought to happen, I looked upon it as of hopeful augury, and was able to encourage the mother to persevere."

I should have little doubt that in this case the only disease was collæmia and slow capillary reflux, with more or less heart failure; but all heart tonics failed till the cause was removed.

It seems to me also that we have here a condition related to that already mentioned on p. 386 as "family periodic paralysis," though here the loss of power was chronic and persistent rather than temporary and periodic. In all such conditions we see mere modifications of the cardiac failure which occurs when an ordinary migraine is complicated by syncope; and thus Dr. Handson's most interesting case was but an exaggeration of the migraine and vertigo on which it supervened. The diagnosis of hysteria is most interesting, as I have always maintained that hysteria is a circulation disease (collæmia plus cardiac failure), and the two cases just narrated would almost suffice to prove this even if they stood alone; but as a matter of fact one finds almost all gradations and intermediate conditions between headache, vertigo, mental depression, nervousness, hysteria, epilepsy and paralysis, just as one also finds all gradations from paroxysmal albuminuria and anæmia of migraine through paroxysmal hæmoglobinuria to Bright's disease, and through paroxysmal glycosuria to diabetes; and thus migraine is a veritable epitome of all these circulation diseases owning a common cause.

Some evidence in favour of Semmola's theory of hetero-albuminæmia is given by the late Dr. Cranstoun Charles in a paper on "Intermittent Albuminuria" (*St. Thomas's Hospital Reports*, vol. xxi.), and he mentions that in one young man he found, just as Semmola had done, some albumin in the perspiration and saliva, as well as in the urine.

The same author mentions several interesting cases of albuminuria associated with high blood pressure, mental depression or headache; one case in which there was albuminuria in the menstrual periods, and another case in which it was associated with constipation, and relieved by blue pill and salines. I have no doubt that the mercury and the salines affected the capillaries all over the body as well as the intestines. He also speaks of the effects of exposure to cold and its possible influence on the skin, and

mentions several other points which are in favour of the metabolic origin of these albuminurias.

I have already said that the cases of albuminuria described by Dr. Dukes are associated with high blood pressure, influenced greatly by diet, and that he himself considers that they often pass into Bright's disease.

I differ from him in believing that such albuminuria and Bright's disease are not due to hyperæmia of the kidneys, but are the result of a failure in metabolism and hetero-albuminæmia, which alone can explain all the facts.

When the failure of metabolism is slight and the hetero-albuminæmia occasional, very slight change in diet, clothing, exercise or climate may remove it, as in the cases I have mentioned; but when it is more severe, and especially when, owing to atrophy of metabolic structures, it has become organic, or still more, if it is complicated by a kidney lesion, these measures will no longer remove all the albumen, and complete cure may be impossible.

The kind of albumen excreted seems also to tell the same tale, for it is now pretty generally recognised that in functional cases as well as in paroxysmal hæmoglobinuria, the albumen in the urine is mostly globulin, which dialyses freely, while in advanced cases with probably distinct and definite kidney lesion, serum albumen is present which will not dialyse (*Lancet*, 1889, vol. ii., p. 1806). Now the late Professor Semmola pointed out many years ago that in early and acute cases there is an excess of diffusible albumen in the urine and blood; while in advanced cases with distinct kidney lesion the albumin in the urine may be almost entirely serum albumen.

The serum albumen passes only when there is a kidney lesion; the diffusible albumin passes at any time, because it is diffusible. Its presence in the urine is a sign of hetero-albuminæmia, just as glycosuria is a sign of glycæmia.

Where diffusible albumen is alone present, the conditions are still functional, and diet treatment, which removes the hetero-albuminæmia, may cure quickly and completely; but where serum albumen is passing, diet will no longer cure promptly, and may not cure at all, for the removal of the hetero-albuminæmia does not do away with the kidney lesion which is now present and allows the serum albumen to pass.

It has been pointed out that pyrogallic acid, toluylene-diamine, &c., when used to produce hæmoglobinuria in animals, do eventually bring about severe nephritis (*Lancet*, 1885, vol i., p. 115).

Is it the substance itself, or its effect on the blood, that produces

the nephritis? Semmola, at least, would probably have attributed a share of the result to hetero-albuminæmia and hæmoglobinæmia. The late Dr. Ralfe suggests (*Lancet*, 1886, vol. ii., p. 764) that functional albuminuria is but a minor degree of paroxysmal hæmoglobinuria; and I have pointed out that in both troubles there are often abundant signs and symptoms of collæmia; and this author himself points out that in functional albuminuria there are frequently bilious attacks, which I should translate by the one word collæmia (see above case of E. H.). He also says that arsenic diminishes the hæmolytic action of the liver and strengthens the resisting power of the red cells; it did not appear to do so in the case of Daniel H. given above (p. 517); but there was severe collæmia, and treatment of this was followed by general improvement. Arsenic, as we shall see in chapter xvi., probably clears the blood of uric acid, and would no doubt in this way affect its quality, but it failed to clear the blood of uric acid in the case of Daniel H., because of its great alkalinity due to his feeble nutrition, and therefore it did no good.

But supposing the uric acid in the blood can thus bring about hetero-albuminæmia, albuminuria, and nephritis, the nephritis, when it has come into existence, will have an important effect on the excretion of uric acid; for anything in the nature of inflammation in the kidney must diminish its alkalinity; and if the alkalinity of the kidney is less than that of the blood and tissue fluids generally, it follows from my first principles (chapters ii. and iii.) that any uric acid that comes to the kidney will be rendered insoluble and retained, instead of being excreted; hence it comes about that though we have plenty (too much) of uric acid in the blood, we have too little in the urine in Bright's disease (see also previous remarks and references on the subject of Uric Acid Infarcts in chapter iii.).

Hence in acute nephritis (but less in chronic disease), no matter what may be the alkalinity of the blood, we get a holding back and retention of uric acid in the body, because the diminished alkalinity of the kidney is unfavourable to its solubility and excretion.

Hence, we have chronic collæmia and its signs, obstructed capillaries, high blood pressure, if the heart is a strong one, slow action of the heart (bradycardia), scanty urine, retention of water in the body and general dropsy, with other signs of collæmia, such as headache, mental depression, tendency to suicide, all of which are well known to occur in Bright's disease.

An interesting case, illustrating some of these points, was admitted under the care of my colleague, Dr. Tooth, at the Metro-

politan Hospital, and he very kindly gave me leave to mention it. A boy, 8 or 9 years old, admitted with subacute nephritis and general dropsy. Urine only 15 to 16 ozs. in twenty-four hours. Measles was accidentally introduced into the children's ward, and this patient, with others, took the disease. The effect was magical. As soon as the fever had reduced the blood pressure, the urine ran up, and was for several days about 80 ozs. in the twenty-four hours, and in two or three days the dropsy had nearly all gone. Here the rise of temperature and concomitant rise of acidity cleared the blood of uric acid, freed the capillaries, among others those of the kidney; the result was a copious diuresis and removal of the dropsy. Now precisely the same can be done with drugs, acids, opium, mercury, any of those in chapter ii. mentioned as causing retention of uric acid, and the result will be proportional to their power over uric acid. In some cases of nephritis I have, with these drugs, altered the pulse rate from about 44 to 80 or above (see fig. 36), at the same time reducing its tension; and with this went increase of urinary water, removal of dropsy, and diminution of albumin. Nature is, however, generally more powerful than any drugs, as the above case well illustrates; but I believe that she acts in the same way by clearing the blood of uric acid, and we know that there are very few granules in the blood in fever.

Another case is that of Wm. S., aged 12, admitted into the Metropolitan Hospital November 26, 1903, suffering from general œdema and albuminuria. On admission his pulse was 96, his capillary reflux 9, and his blood pressure 150 to 160. The apex beat of the heart was in the left nipple line, and the first sound was long and the second sound loud. Specific gravity of urine 1014 and it contained albumin to the extent of 1½ per 1,000 (Esbach). He was put on a mixture containing iodides and chlorides, a diet containing fish, and fluids were reduced to 1½ pints in twenty-four hours. He went on well, and on December 8 the capillary reflux was 6 and the blood pressure only 120, while the albumin had fallen to ½ per 1000.

On December 15 the pulse was 72, the capillary reflux 6, and the blood pressure 110 to 120, he was taking little more than one pint of fluid in the day, and the albumin was often only a mere trace. He was soon allowed to get up and went out on December 31.

This case improved somewhat rapidly, for it is characteristic of the young to have rapid metabolism, and once the fire was got to burn up all went well.

No doubt in three or four months he would get free from

albumen, and if he was able to keep himself free from unnecessary uric acid would probably have no more trouble of this nature.

In connection with the treatment of these conditions I have been greatly interested by an article in the *Lancet*, 1905, vol. ii., p. 1394, by Drs. H. D. Rolleston and J. Atlee, on the "Extraordinarily Rapid Diminution of Renal Dropsy under Citrate of Caffein." The dose of caffein was 7½ grs. three times a day, and this no doubt cleared the blood of uric acid, thus freeing the capillaries, lowering the blood pressure, and producing, as is recorded, an enormous diuresis. In this it acted just like uric acid itself or any other substance that would similarly clear the blood by interfering with solubility, acting, in fact, just as an excess of lime thrown into water carries down in precipitation any lime previously in it. So uric acid or caffein added to blood does not remain in solution, but carries down with it by uric-acid filter action (see chapter v.), all the uric acid previously in solution in the blood. Then the freeing of the renal capillaries and the diuresis were results of this, for the only thing it is necessary to do to remove dropsy is to clear the blood of uric acid, and Nature herself, as we have seen in some of the cases previously mentioned, does this most effectually by means of fever. And for years she has been telling us the same thing in the well-known fact that uric acid and water always move in opposite directions both from hour to hour and day to day.

Annie B., a washerwoman, aged 31, admitted into the Metropolitan Hospital on March 5, 1906, suffering from subacute dermatitis and more or less general erythema and exfoliation. She said that she had been suffering from it for about a month, that it had begun on the arms and spread to the body.

On admission the temperature fell nearly to normal in the morning but rose to 101° F. in the evening. The urine, specific gravity 1014, contained no albumin. She was put on bicarbonate of soda and a milk diet, and the skin condition began gradually to improve, so that by the 16th the temperature was constantly under 100° F. On the 16th, however, it was noted that the urine had a specific gravity of 1026 and contained a trace of albumin; on the 20th this had increased to a heavy cloud, and on the 21st there was 1¾ per 1,000 of albumin. On March 20 the pulse was 64, blood pressure 140, flattened 180.

On March 23 the bicarbonate of soda was left off, but the albumin went on increasing for some days after this, reaching its highest point, 2¾ parts per thousand, on the 26th. On March 27 the pulse was 76, the temperature normal, but the urine was found to

contain hyaline and granular casts. On examination of the abdomen nothing abnormal was found; the right kidney was just able to be felt, but it was not tender. On March 29 and 30 the albumin had fallen to $1\frac{3}{4}$ per 1,000, but as it seemed to be going down very slowly, a mixture of chloride, bromide, and iodide was given on the 30th.

On April 3 the albumin had fallen to 1 per 1,000, with a specific gravity of 1027, and on April 11 it was only $\frac{1}{2}$ per 1,000, and a specific gravity of 1023.

There was no return of the dermatitis, a few days later the urine was found to be free from albumin, and the patient was allowed to leave the hospital.

May 8, 1906.—The patient came to the hospital to-day and brought a sample of urine, specific gravity 1020, which was found to contain a good cloud of albumin. She had not been taking any medicine, and had apparently relapsed to some extent. Her capillary reflux, taken on the chest, was 7 to 8 half seconds, blood pressure 160, flattened 200. She was advised to take the chloride mixture again and to report in about a month's time.

I think that the following case recorded by Dr. A. F. Elliott in the *British Medical Journal*, 1906, vol. i., p. 920, will form an interesting parallel with this :—

The patient, aged 6, was first taken with arthritis, and this was followed by purpura and abdominal pain with vomiting, which again was followed by diarrhœa. The urine became scanty and contained much blood and albumin, and this again was followed by œdema of limbs, chest and face, uræmic convulsions and death. It is interesting that both the father and mother of this patient suffered from rheumatism.

In this case we had an arthritis to begin with instead of a dermatitis. This arthritis was converted into collæmia by gastro-intestinal troubles, and eventually the collæmia became complicated with heart failure, general œdema, œdema of the brain and uræmic convulsions. If my hospital case above recorded had suffered from gastro-intestinal trouble, no doubt her collæmic trouble, her albuminuria and œdema would also have been more severe.

Here we have instances of precipitation diseases being cured by solvents, or conditions that acted as solvents, and collæmic diseases resulting.

The case of Annie B. illustrates the old belief in the danger of curing skin diseases too quickly, also the belief of Semmola and others as to the part played by the skin in the causation of albu-

minuria. There was very active combustion in the skin during the dermatitis, but the alkali which cured this converted it into collæmia and defective combustion, and albuminuria was the result. Obviously to stop the albumin we must use precipitants and may have to bring back the precipitation disease.

It may be asked why, in chronic interstitial nephritis, while there is still high blood pressure, do you get no holding back of water and no dropsy?

I have suggested, as the result of my own observations on the matter, that in chronic nephritis the collæmia is greater in the alkaline tide of the morning, and, as a result, the pulse is slower and the urine more scanty at this time. Later in the day—the evening and night—collæmia is less, the capillaries are relatively free, and a considerable diuresis makes up for the scanty excretion of the other hours (see quantities of urine per hour in table given by Saundby, previous reference, p. 15). For a case in which this was so see *Lancet*, 1890, vol. ii., p. 133.

In this way there is no retention of water in the body in chronic Bright's disease, for though the capillaries are obstructed and the tension high, the heart is equal to its work, and especially at night the circulation is free. In acute Bright's disease, the sudden obstruction of capillaries may overpower the heart and dropsy results. In all cases I believe it is a struggle between the heart and the obstructed capillaries; if the heart fails there is dropsy, if it wins there is none (see Marey's observations, quoted in chapter v.).

There are no doubt two factors in dropsy: (1) that water in the blood cannot get past the kidneys, or for that matter the skin or any other excreting glands, because of the block in the capillaries; and (2) that the water in the tissues is only very slowly taken up into the blood. This is well shown by the experiments of Reechel (*Centralbl. für inn. Med.*, October, 1898), who infused saline solution and showed that in renal cases it took a very much longer time to be absorbed from the tissues than in healthy individuals.

No doubt it would be much slower in all takers of meat and tea than in those who abstain from them, just as the capillary reflux itself is slower in the self-poisoners.

Slow capillary reflux always means defective circulation, defective nutrition, defective interchange between the blood and tissues, and defective combustion; it is really albuminuria, Bright's disease, glycosuria, diabetes, polysarcia, obesity, œdema or dropsy in embryo; and it may develop into any one of these or several of them, more or less combined, as is sometimes seen.

The capillary reflux is thus the index not only of the circulation, but also of the nutrition and combustion of the body; and when we know the cause of the defective circulation, and while it is still functional and due to collæmia merely, we can at once control both it and its effects; and in all cases pathology is thus seen to be a mere exaggeration of physiology, as collæmia controls formation of urea and excretion of water in the latter.

If we wish to understand dropsy thoroughly we must study most carefully the relation between the excretion of uric acid and water in the physiology of every-day life; in the morning hours even in physiology there is more water in the blood and tissues than in the evening, and in the uric acid headache the water in the tissues often increases so as to be visible; and between this and dropsy, either cardiac or renal, the difference is only one of degree: in cardiac dropsy the water fails to pass the kidney because the heart has lost the power necessary to drive the blood through the kidney vessels; in Bright's disease the heart power may be undiminished, but the kidney vessels are obstructed by uric acid. Dropsy is commonly due to both conditions, *i.e.*, collæmia plus cardiac failure.

In chronic nephritis, also, the alkalinity of the kidney is less reduced than in the acute disease, hence the holding back of uric acid and consequent collæmia is relatively less.

Collæmia is more severe in sudden and acute cases, and this corresponds with the relation of uræmia, the poison of which is, I believe, simply uric acid; and its symptoms, at least the most prominent ones, are the results of the action of this poison on the vessels, and so on the circulation of the brain. And by measuring the capillary reflux and blood pressure at the same time the real causation and sequence of events can be proved.

Before the attack, as is well known, the urine is often extremely scanty, and the pulse may be as slow as 40 (intense uricacidæmia and collæmia). The case in which I altered the pulse rate from 44 to upwards of 80 had slight convulsions, severe headache and other signs of uræmia at the time of admission under my care.

The very close parallel between the symptoms of collæmia and those of uræmia has long interested me, and I believe that till a fatal lesion is produced, I have the same power over the one as the other. Let us look for a moment at the main symptoms of uræmia, and first, epileptiform convulsions. I have shown that similar convulsions may be the work of uric acid; then as regards headache, giddiness, drowsiness, cold skin, cold sweats, local arterial

spasms, "dead hand," vomiting, slow high tension pulse, scanty urine — these are merely the signs of the uric acid headache (migraine). Amaurosis, again, is probably an exaggeration of the well-known eye symptoms of migraine.

I have obtained considerable quantities of uric acid from the blood of uræmic patients, as ·0025 per cent. from a case under the care of my colleague, Dr. Tooth, at the Metropolitan Hospital, and ·0021 from a case under the care of Dr. R. Kirk, of Glasgow, who kindly sent me the specimen, and ·0048 per cent. from a patient of my own at the Royal Hospital for Children and Women, who was 17 years of age, and had a large, pale kidney. Her temperature was 105° F. soon after the blood was drawn, and when a little later she came out of the coma she complained of a severe headache, in many respects resembling that of uric acid. In the first case the temperature was 103·8° F. at time of cupping, and the amount found was probably only a fraction of the quantity in the blood when the uræmic symptoms began; but even so, it is nearly four times as much as is found in other diseases associated with fever, *e.g.*, ·00067 per cent. in pneumonia, with temperature 102° F.

We have here, then, as I have shown, all the causes which produce collæmia, and all the signs of its presence, and, further, all the drugs, which do good in treatment (opium, acids, &c.) clear the blood of uric acid, while bleeding mechanically reduces the tension and pressure by means of which the uric acid fatally affects the nerve centres (see chapter vi.).

The great value of morphine in eclampsia is further evidence of the same thing, and everything that does good in these serious results of collæmic circulation either lowers the blood pressure mechanically, as bleeding or purging, or clears the blood of uric acid, which is the action of morphine, and it acts in exactly the same way in the less severe conditions of collæmia, such as migraine and depression.

Thus in a case under my care I believe that I can trace all the factors that led up to a fatal uræmic convulsion.

Lydia M., aged 44, admitted into the Royal Hospital for Children and Women, on April 2, 1897, suffering from chronic Bright's disease, heart failure and dropsy.

On admission, temperature 97° F., pulse 80. High tension.

I saw her two days after admission and found that she had been put on pulv. jalapæ co. and a pill containing mercury, squill, and digitalis, to be taken three times a day. Heart's apex beat fifth

space, 1 in. outside the mid-clavicular line; the first sound was long or reduplicated, and the second sound loud and sharp both at the apex and base.

Her temperature had risen to normal, pulse 84, and the bowels were open two or three times every day.

Urine had specific gravity 1012, and contained a considerable amount of albumin.

April 8 and 9 there were some teeth troubles, ending in stomatitis.

April 10, pill left off, and a mouth wash given.

The pulse had gradually slowed down, no doubt owing to the digitalis and the rest in bed, to 72 on 7th, 66 on 8th, 60 on 9th, and 56 on 10th, and it now further slowed to 52 on the 11th, and 42 on 12th April.

The first part of this slowing was no doubt due to the rest in bed and the digitalis, and with this improvement in heart power the dropsy had all cleared up.

On the 11th and 12th there was very marked stomatitis, and the pulse slowed still more to 52 and 42 in spite of the digitalis having been left off, and showed still higher tension.

I saw her for the last time on the afternoon of 12th, after the resident medical officer, Dr. Key, had noticed some twitching of the face.

The pulse was then regular and only thirty-six in the minute, and showed very high blood pressure, and the patient was dull and inclined to be drowsy.

I concluded that she was suffering from severe collæmia as a rebound after the mercury, and ordered some iron and other drugs with a view to stop this and lower the blood pressure.

Before these had had any time to act, however, at 6.30 p.m. the same evening she had a severe convulsion fit, in which she died.

Now these symptoms tell their own tale.

On admission she had collæmia with subnormal temperature and quick pulse (heart failure) and their result—dropsy.

A week's rest in bed, with the help of squill, digitalis and mercury, restored the temporarily disabled heart, its rate of action slowed to normal, and the dropsy disappeared.

Then came the stomatitis, necessitating the stopping of the mercury, and the natural result was a post-mercurial collæmia or rebound, and in some of the cases that follow, it will be seen that I now take precautions to prevent this unfortunate result so far as it is possible to do so.

But the heart was now fairly strong and so the pulse got slower

and slower as the pressure rose, and the high pressure in the skull produced first twitchings of face muscles, then drowsiness, and finally a convulsion, which was fatal.

I now regret that I did not order her to be bled on the afternoon of the 12th, when things were clearly very threatening; but if she had survived the first convulsion this treatment, the only one I expect much from in acute uræmia, would no doubt have been carried out.

In a case of uræmia more recently under my care at the Royal Hospital for Children and Women, Louisa L., aged 58, there was a blood pressure of 180 and a capillary reflux of 10. The blood contained granules in proportion to the red cells of 1 to 2, and blood drawn by venesection yielded ·0029 per cent. of uric acid.

There is an interesting note on the relief of the severe head pain of some high blood pressure conditions of Bright's disease by withdrawal of cerebrospinal fluid by lumbar puncture in the *Lancet*, (1902, vol. i., p. 609). The relief was often only temporary, but the interesting bearing of the facts on the pathology of uræmia is obvious.

I will now give a few notes of some of the more interesting cases of Bright's disease that have come under my care.

Charlotte W., aged 15, admitted at the Royal Hospital for Children and Women, October 28, 1890. She had been seen by my colleague, Dr. Wheaton, on October 22, at the Surrey Dispensary, complaining of numbness and loss of power in the right hand and of "fainting fits."

On October 26 she was quite comatose for some time after a succession of convulsions.

On admission she was noticed to be quiet and drowsy and slow in answering questions. The face was pale and the eyelids puffy, and there was some œdema of the back and chest.

Pulse 66, high tension, with a well marked W tracing, as in fig. 35 A. Heart's apex outside left nipple line, first sound long (? systolic murmur), second sound very loud both at apex and base. Lungs, a few râles at both bases. Some little ascites. Urine 1025, some blood, and albumin 7 per 1,000 (Esbach).

October 30 she was given pulv. jalapæ co., a hot air bath at night and some citrate of potash with a little nux vomica.

October 31.—Some headache this morning, but no fits since admission.

November 1.—Pulse, morning, 48; still some headache. Pulse, evening, 60. Heart, second sound still very loud.

November 3.—Pulse, morning, 48; evening, 48.

November 6.—Pulse, morning, 50; evening, 44. Citrate of potash left off and salicylate of soda given after meals with acid mixture (nitro-hydrochloric acid) before meals.

November 8.—She had a little diarrhœa, so all drugs were left off.

November 9.—Pulse, morning, 54; evening, 54.

November 10.—Salicylates and acids begun again yesterday. Pulse, morning, 60; evening, 60.

November 15.—Pulse, morning, 72; evening, 72.

November 17.—Salicylates and acids left off. Pulse, morning, 72; evening, 86, and a tracing now showed comparatively little tension.

November 27.—Pulse rate had fallen again, and was, morning 56; evening, 68. Soon after this she was allowed to get up and the pulse rate quickened in consequence.

The albumin, which was very high in the specimen on admission, was not much more than 1·0 per 1,000 in a 24 hours specimen. On November 10 and 13 it was still 1·0 per 1,000, but on the 17th it was ·5 per 1,000, and it remained at or about this amount during the rest of her stay, with the exception of the 24th, when it was ·6 per 1,000.

The urine at first contained fairly numerous casts, hyaline, with granules and degenerate epithelium.

She was given fish on November 27, and she went on well, having no fits, no headache, and no increase of albumin, and she was allowed to go home on December 5.

This case seems to show, as does also one previously mentioned in chapter v., that citrate of potash neither quickened the pulse nor lowered its tension, while salicylate of soda and acids did both very decidedly, though it tended to slow down again after these drugs were left off; and the most decided fall of albumin coincided with their action and the lowered blood pressure they produced.

Alice M., aged 8. Admitted into the Metropolitan Hospital December 4, 1891.

December 5.—Pulse, morning, 68. Tracing shows very high tension, predicrotic wave rising above the upstroke. Urine, 18 ozs., 1018. Albumin 5 per 1,000 (Esbach). Fairly numerous hyaline and granular casts. Given acid and salicylate mixtures as in the previous case.

December 9.—Much better in self. Pulse 84, and first wave is now well below the upstroke. Urine, 24 ozs., albumin little more than a trace.

After this albumin remained about a trace only, and she went home at the beginning of January.

All drugs were left off on December 23, and the pulse on December 27 had fallen to 58.

Ada P., aged 16. Admitted into the Royal Hospital for Children and Women on November 23, 1893.

She had recently recovered from scarlet fever. Urine, 40 ozs. in 24 hours, containing 2·0 per 1,000 of albumin (Esbach).

Casts very numerous, large hyaline and granular, some fatty and some epithelial.

She was put on iodide of potassium and nux vomica, and was given hot air baths frequently, and aloes and iron pills for the bowels occasionally.

The urine became alkaline, the temperature continued subnormal, and she remained for a long time without improvement or decided decrease of albumin.

After she had been in more than two months, it struck me that the hot hair baths were really doing harm, causing weakness, both general and of the heart, depression, alkaline urine, increased alkalinity of the blood (see fig. 72 as to the effect of a Turkish bath), and subnormal temperature; that, in a word, instead of increasing the combustion and metabolism of the body we were diminishing it.

Here there was a large amount of uric acid, and there was not enough alkali to hold it all in solution; hence it produced collæmia and did harm; and increased weakness of the heart would similarly tend to diminish combustion.

The baths were accordingly reduced and left off, and the temperature then rose to normal, and remained there till she went out in February. With this she improved decidedly, and the albumin was reduced to a trace when she left.

Her case left on my mind the impression that the hot hair baths did harm, and that if we had left them entirely alone and trusted to drugs, such as the iodide of mercury, which clear the blood of uric acid we should have got rid of her albumin much sooner.

In future I shall take the temperature as my guide, and refuse to believe that any treatment is doing good and increasing the metabolism of the body while the temperature remains subnormal; and, indeed, it is an important characteristic of the best action of the iodide of mercury in these cases that as the pulse softens and quickens, the temperature rises to normal and remains there.

Isabel M., aged 46. Admitted into the Royal Hospital for Children and Women on June 14, 1894.

She complained of general œdema and shortness of breath with occipital headache.

Temperature was 102° F. and pulse 78 in the evening and 60 in the morning, being thus very slow relatively to the temperature. A tracing showed a very high first wave, and took 4½ ozs. pressure to develop it.

The heart's apex was displaced to the left beyond the nipple line, its impulse was forcible, and the second sound everywhere loud.

There was some twitching of the arms.

Urine 1020, and contained albumin and blood.

She was put on milk diet, iodide of potassium and nux vomica.

June 18.—Urine 89 ozs., albumin 2 per 1,000 (Esbach) and a little blood. A few large hyaline casts with epithelium granules and fat upon them.

Pulse 84, temperature 99·6° F. Still some occipital headache, with nausea and occasional vomiting.

Mist. hydrarg. perchlor. cum pot. iod. given in place of the other iodide mixture.

June 28.—Urine 54 oz. (there is little or no œdema left, *i.e.*, there is no more water to be run out of the tissues and blood), specific gravity 1010, acid.

Temperature 99° F. Pulse 90.

There were now some signs of salivation, so I cut off the mercury and put on the iodide of potassium again.

July 5.—Urine 50 oz., specific gravity 1010. Albumin (Esbach) ·5 per 1,000.

July 7.—Pulse 80—90, lower tension and only 3½ oz. pressure is now required to develop the tracing.

July 17.—Urine 61 oz., 1010, acid, albumin only a trace.

No symptoms.

July 18.—Allowed to go home and given the iodide of potassium mixture to continue.

I concluded that her troubles on admission were due to uræmia and that we drove it off by clearing her blood of uric acid, relaxing her pulse and freeing her metabolism, so that her albumens were combusted, and not eliminated unchanged.

Lily T., aged 5. Admitted into the Royal Hospital for Children and Women, February 23, 1894.

She had general anasarca, her face was puffy, and there was a history of scarlet fever two years ago.

Pulse 60, high tension. Temperature 99·2° F.

First sound of heart long or reduplicated; second sound loud.

Urine 20 oz., smoky, 1018.

Albumin (Esbach)	2 per 1,000	=	18·4 gr.
Urea	1·4 per cent.	=	129 ,,
Uric acid	·04032 per cent.	=	3·7 ,,
Relation of albumin to urea ...	... ...		1—7.
,, uric acid to urea ...	... ...		1—35.

Casts numerous with much epithelium.

Here we have subacute Bright's disease with a large amount of uric acid in the blood, accounting for the slow high tension pulse, but no large excretion in the urine owing to the irritation of the kidney interfering with its solubility and preventing its passing, as it usually does in physiological conditions, from the blood into the urine.

With this we have scanty urine, low urea = 3·7 gr. per pound, her weight being 34 lb. and a considerable excretion of albumin, equal to 1 gr. for 7 gr. of urea; and with the cold pale skin and anasarca we have every sign of obstructed capillaries and consequent diminished combustion and its results.

She was put on the mist. hydrarg. perchlor. cum pot. iod., with milk as her only food.

She went on well, and on March 2 her urine was 50 oz., specific gravity 1020, containing 1·5 per cent. of urea = 375 gr. Albumin a mere trace, too small to estimate. Temperature normal. Pulse 120, soft. Surface warm.

Here was indeed a different state of things.

Her urea had increased to 11 gr. per pound and the albumin had diminished to such an extent that it could not be accurately estimated, while her diet had not altered.

March 19.—Urine 18 oz.; there was no anasarca.

Urea	1·8 per cent.	= 149 gr.
Albumin	·5 per 1,000 (Esbach)	= 4·1 ,,
Albumin to urea		1—36.

April 7.—Is now up and about. Urine 26 oz., specific gravity 1020, acid. Albumin too small to estimate, say ·25 per 1,000 = 3 gr. Urea 2·2 per cent. = 263 gr. = 7 gr. per pound. Relation of albumin to urea 1—87.

She was now on milk diet. She went on perfectly well and was allowed to go home.

If she went on well and had no accident such as over-feeding or exposure to cold, the albumin would in eight to ten months have completely disappeared and no one who then examined her urine would ever guess that she had had Bright's disease.

With regard to the large excretion of urea on March 2, we can now see from the experience we have had with the effects of uric acid on metabolism, and especially its effects on the causation of fatigue and the excretion of urea during and after exercise (figs. 46 and 47), that this excretion was a measure of her previous defective metabolism.

It was not due to any increase of food or to better assimilation of food, for food and assimilation continued the same, and yet the high urea did not last, but on April 7 urea was 7 gr. per pound as against 11 gr. per pound on March 2.

It is clear, therefore, that this high urea about March 2 was the result of her previous collæmia and defective metabolism, of which, as I say, it was a measure, and represented the imperfectly metabolised nitrogen which was accumulating in her muscles and other tissues, while their circulation was obstructed by uric acid.

But as soon as the blood was cleared of uric acid her circulation was set free, combustion became more complete, and the large excretion of urea represented the products of the previous incomplete metabolism.

Here we have merely an enlarged edition of what we have already seen to occur in the physiology of fatigue, where the collæmia produced by heat and perspiration obstructs the capillaries and reduces metabolism, causing a fall of urea; then later on, when the circulation has again become free, we get a rise of urea which more than compensates for the fall of the previous day (see figs. 46 and 47, and p. 378).

In both conditions, fatigue as well as Bright's disease, we have only to get rid of the collæmia to get a free circulation and metabolism and a complete reversal of all the effects of the obstructed circulation.

With regard to the future of such cases, I will now shortly mention the after history of another case, Susan B., aged 13, who was treated in the same way as some of the above cases, and like them discharged with the albumin reduced to a mere trace.

I first saw her on January 19, 1891, and she left the hospital for a convalescent home on April 4.

Her mother seemed a sensible woman, and I impressed upon her the great importance of giving her no animal food except milk, of clothing her in flannel from head to foot, and guarding against exposure to cold and wet.

She came to see me once a month, and in October, 1891, I have a note that at this and the previous visit I was unable to detect any albumin in the specimen brought.

In 1892 this improvement continued, and she was now growing a strong and healthy-looking young woman.

In 1893, she had, during some cold and wet weather, a slight relapse; there was a trace of albumin in the specimen brought, and she had not been feeling so well and looked a little puffy again.

Bear in mind here the direct effect of cold on the circulation of the skin and also its indirect effect through precipitating collæmia.

I put her on iodides and she soon got all right again, and the urine remained free from albumin as before.

In 1894 this condition continued, and I again began to regard her as completely cured, provided she kept to diet and regulations.

In the spring of 1895, however, she returned with some albuminuria, and had also some *malaise* and the general signs of collæmia and defective combustion.

This time she had to confess that she had been doing wrong, she had been doing some work, and what was worse, had been eating some meat.

This was a disappointment to me, as I had begun to look upon her as cured; but after all it is nothing more than would have occurred if her trouble had been migraine instead of morbus Brightii; in both diseases immunity depends upon a steady continuation of the diet, the moment the introduction of uric acid is increased the trouble returns. If she had been content with her milk diet she could have worked hard without any harm; but she went out to work, and was, I fear, practically compelled by circumstances to eat meat as others did.

I have again seen her more recently; she has been keeping strictly to diet, refusing to indulge even on Christmas Day. Her appearance does the diet every credit and the urine is quite free from albumin, and has specific gravity of 1017.

I have since seen this patient several times in 1896 and 1897. She keeps faithfully to the diet; there has never been any albumin, and the specific gravity runs from 1015 to 1020, and collæmia, being impossible, cold weather has been unable to affect her.

In a patient suffering from chronic arthritis, periostitis (believed by the late Mr. Walsham, who saw him with me, to be rheumatic), and also from parenchymatous nephritis, I was interested to find that both troubles fluctuated together; that when he had increased trouble in his joint he also had increase of albumin or even recurrence of blood in his urine, so that it looked as if the condition (? rise of acidity) which drove the uric acid into and produced increased irritation of his joint, had driven some also into the kidney (gout of the

kidney) and increased the renal trouble, and I think we must not altogether lose sight of this possibility; but, on the other hand, it is clear that any arthritis which is due to uric acid is due to a fluctuation of uric acid—that is, there is first an excess of uric acid in the blood (collæmia) and then some rise of acidity precipitates it on the joint (see chapters xv. and xvi.); and though both troubles appeared to get worse together, the increase of albumen may have been due to the collæmia in the way I have suggested and not to the local irritant action of uric acid in the kidney.

I was greatly interested in this case because, when I put him on a milk diet, both his arthritis and nephritis steadily improved together, and he was greatly pleased with the result of this treatment. I have no doubt that both were due to uric acid, the action being direct in the arthritis, probably indirect in the nephritis.

Another case similar to those given is that of Edwin R., aged 52, admitted into the Metropolitan Hospital, April 1, 1896, suffering from swelling of the legs and headache for two weeks. There was a history of some kidney trouble on and off for about six years.

On admission the face was puffy and there was some œdema of the legs. Temperature subnormal. Pulse 90. Heart's apex beat well outside the left nipple line. Impulse diffused and heaving.

April 4.—Urine full amber, pale deposit, 1020, acid, quantity 30—48 oz. per day.

Urea 2·2 per cent. Albumin (Esbach) 1·5 per 1,000. Relation, 1—14. Numerous casts, hyaline, with granules, degenerate epithelium and fat.

Pulse 100. Diameter of R. radial aretry lying down = 2·2 mm. On milk diet. Given mist. hydrarg. perchlor. c. pot. iod., ter.

April 8.—One pint of milk added. Mixture to be taken *quater in die*. R. radial diameter 2·2 mm. Pulse rate 112.

April 11.—Urine shows some slight increase in quantity.

Blood examined, 4 p.m.:—

$$\frac{\text{Hæmoglobin}}{\text{Cells}} = \frac{\text{60 per cent.}}{\text{106 per cent.}} = \text{blood decimal} = \cdot 56.$$

April 13.—Urine 68 oz.

April 16.—Urine 72 oz., 1014, acid.

Urea 1·3 per cent.
Albumin ·3 per 1,000 } 1—43.
R. radial diameter 1·7 mm.

April 20.—R. radial diameter 1·7 mm. Albumin reduced to a trace too small to be estimated.

April 28.—Up and about in the ward.

Blood to-day :—

$$\frac{\text{Hæmoglobin}}{\text{Cells}} = \frac{65}{103} = \cdot 63.$$

Here, as the result of three weeks and three days on iodide of mercury and diet, we have the urine increased and the dropsy removed; the blood pressure lowered, as shown by the fall in the diameter of the radial artery, the capillaries freed and combustion stimulated, as shown by the fall of albumin, which was reduced from a relation to urea of 1—14 down to something less than 1—43, and lastly, we have a distinct improvement in the quality of the blood itself produced here, just as in chlorosis and by the very same drug (see fig. 57), showing conclusively that all the above results of the removal of collæmia by iodide of mercury were due to a general improvement of nutrition and metabolism. This is but the same effect on a larger scale which can be produced any day and in anyone in the physiology of fatigue.

This patient continued to do well, and the iodide of mercury mixture was given three times a day. He was put on a uric-acid-free diet containing milk, and cheese with bread, puddings and farinaceous dishes *ad lib.*, and a little vegetable and fruit. When sufficiently instructed in this diet he was allowed to go home, continuing the mixture, which was later on changed for one containing iodide of sodium and nux vomica, which he kept on with together with the diet for a long time.

November, 1896.—Is keeping faithfully to the diet, which he likes, and is much pleased with the improved health he has gained. I have examined several specimens of urine lately and have found no trace of albumin in any.

Here there was a comparatively quick reduction of albumin at first, as it fell to a trace in the third week of treatment; but that trace remained for several months, only gradually diminishing and becoming invisible. This shows the two origins of albumin in such cases: the larger amount, which disappeared early, was the albumin of defective combustion, which was at once metabolised into urea when the capillaries were cleared and the fire burnt up; the small lingering trace was the organic albuminuria, the measure of the injury done to the kidney, and possibly, as the late Professor Semmola suggests, to the blood albumens themselves by the experiences they had passed through, and these injuries take some time to repair and pass away. In this case the blood improved along with the improved metabolism of albumin.

If in all cases the iodide of mercury acted just as it did in these, I should have little doubt of my power to cure every case of Bright's disease that came before me; but as this is unfortunately not the case, I must mention the other side of the picture—the cases in which I fail, and the reasons of such failure.

If mercury disagrees, if it causes salivation, dyspepsia, or diarrhœa, it quite fails to control uric acid collæmia and is useless in the diseases which are due to it; iodides also may cause iodism and have to be left off for this reason; and in some cases we are deprived of the use of these drugs by such results, though, as will be seen further on, there are ways of getting over some of these difficulties.

In this case we should remember the effects of salicylates with acids, or with opium in small doses, for though less powerful than iodide of mercury, they may succeed.

But even when the iodide of mercury does not cause salivation or upset the stomach and intestines, it may fail to cure, and that for a reason which will be best illustrated by a case in which it twice succeeded and then failed to reduce the albumin at all.

Edgar G., aged 18, first admitted into the Metropolitan Hospital on September 18, 1895. There was a history of Bright's disease extending over two years.

He had now considerable general anasarca and ascites, and the urine contained 7 to 8 per 1,000 of albumin.

He was given iodide of sodium with nux vomica and occasional doses of calomel, but he did not improve much.

October 20.—Abdomen tapped and 7½ pints of fluid withdrawn.

October 23.—Given mist. hyd. perchlor. c. pot. iod. with nux vom. and digitalis. Pulse 92. Temperature subnormal.

October 25.—Abdomen again tapped and 8½ pints withdrawn. Pulse 104.

October 27.—Temperature rising towards normal. Urine increasing. Pulse 92, and this was the beginning of a marked improvement, the iodide of mercury coming into action and being aided by the nux and digitalis, and last, but not least, by the tapping and removal of ascites.

November 1.—Much better; œdema all gone; is passing 40—70 oz. urine. Pulse 88.

November 19.—Pulse 88; urine 66 oz.; specific gravity 1011: neutral albumin ·1 per 1,000; urea 1·1 per cent.; relation 1—91; allowed to get up.

December 5.—Left hospital; albumin a mere trace; urine plentiful; advised to keep always on milk diet.

May 20, 1896.—Readmitted with a relapse; had been at work as a stable boy and was not able to get proper food; temperature subnormal (sign of defective combustion); general anasarca and slight ascites as before.

May 22.—Urine 16 oz.; amber, turbid, 1024, acid.

Albumin (Esbach) ·625 per cent. = 46·2 gr.
Urea ... 3·7 per cent. = 279 gr. } 1—6.

Microscope shows very numerous casts; much degenerate epithelium and fat; very different from the urine when he went out in December last.

He again improved on the same iodide of mercury mixture with nux and digitalis, and after the ascites had been tapped once or twice, but he did not respond to the drugs so quickly, and there were evidences of increasing cardiac dilatation and quickening of the pulse.

However, by June 13, and especially after a paracentesis abdominis on June 1, the urine increased to 48, 56, and 60 oz., began to contain little more than a trace of albumin, giving a relation to urea of 1—25 and less.

After this the amount of albumin became so small that it could not be estimated, and the urine at the beginning of July went up to 98 and 106 oz.

He now again went out, having received full directions and cautions as to the importance of diet; but this time he was too weak to work, and being dependent on others he had more than ever to take what food he could get, and then he was sent to a convalescent home and fed on soup, fish, meat, and what is generally called the fat of the land.

He did not improve on it, however, but again got ascites and anasarca and was confined to bed, and then he got some sloughing sores on his legs, when an attempt was made to run off the fluid from the skin with tubes; and then he was again sent back from this convalescent home to the hospital.

But this time I could do nothing for him, though a more suitable diet did some good and the sores on his legs healed. The drugs that had been useful before now failed either to increase the urine or diminish the albumin, and even repeated tappings did not give them a start. He remained like a marsh, full of water, and the water ever slowly rising and putting out more and more completely the fires of combustion.

The explanation of this is fairly simple if we look upon Bright's disease as a failure of combustion, which again is due to defective

circulation, which in its turn is the result of collæmia overpowering say a normal heart (acute Bright's disease), or as in this case a heart which grew gradually weaker and weaker as the general strength and nutrition failed.

It is obvious that with a given amount of collæmia we shall get ever greater and more disastrous effects on the circulation, nutrition and metabolism of the body as the nutrition and power of the heart fail.

Then the scanty urine is a measure of the obstruction to the circulation in the vessels of the kidneys, and this is an index of the larger and more important obstruction to the circulation in all the great metabolic tissues of the body, which is the cause of the defective combustion.

Now something of this kind happened in the case of Edgar G. With his first attack his trouble was almost entirely functional—a defective combustion due to acute collæmia. His heart was fairly well nourished, his tissues were young and moderately well formed and sound, and as soon as the collæmia was cleared up by drugs, circulation and combustion were resumed, and he was again in a position to deal with all the albumens in his food. Hence urea increased and albumin in the urine diminished till only a trace was left, and that trace was due to some little irritation in a few cells of the kidney, resulting from the passage of the albumin, while certain cells in the liver, skin, &c., had suffered a corresponding irritation and were also slowly undergoing regeneration.

But with these exceptions he was a sound man, and had only to make further collæmia impossible, by living on a uric-acid-free diet, to remain well and strong and be like the previously mentioned cases, completely cured of his disease.

Unfortunately, however, he was unable to control his diet, so that collæmia was allowed to return, and he was once more subjected to a severe attack of defective combustion, with further damage to blood, metabolic tissues and kidneys.

Thus we find that with each attack he recovered more slowly and with greater difficulty; in his first attack a mere clearing up of the collæmia by iodide of mercury sufficed to free the capillaries of the kidneys and run off the water, the fires burnt up and the albumin was reduced to a trace.

At the next attack nutrition is not so good, and defective nutrition means defective power of muscle, especially of that most important muscle the heart; hence something more must be done besides clearing up the collæmia, and nux vomica has to be added to

strengthen the heart; also there is now a distinct falling off in the nutrition of the kidneys and metabolic tissues.

Nevertheless he again becomes solvent and can metabolise all the albumens of his food, and has once more a chance of life if he can control his diet.

At the next attack, however, things are still worse, and now both digitalis and nux vomica are required to get the heart up to its work; but the fires burn lower, the water rises higher, and the difficulty which the drugs meet with in clearing up the collæmia is owing to the increasing defectiveness of nutrition.

And so the issue is for some days in doubt whether the heart will get sufficient power to drive the blood through the kidneys even when the collæmia has been removed; if it fails to do so the water will rise ever higher and higher, and the fires will soon be extinguished. Under these circumstances comparatively small matters suffice to turn the scale one way or the other, either for the heart or against it.

And one of these is no doubt the presence of a little fluid in the great serous cavities which, by hampering the function of the lungs, the heart, the diaphragm, or otherwise impeding the circulation in the digestive viscera, the liver, the kidneys and abdominal vessels, may turn the scale against the heart and lead to its further dilatation, failure, and final defeat.

Hence we see that the last time the iodide of mercury succeeded in the case of Edgar G., it only did so with difficulty and after every help had been given it by clearing the fluid out of the peritoneum; and I have had several hard-fought cases in which the fluid in one or both pleura had to be removed in the same way; but each time the effect became less and less, the fires burnt lower and lower as the metabolic tissues wasted, and the water rose in them ever higher and higher, and the heart muscle got weaker and less well nourished.

This heart failure is the final and absolutely hopeless stage of all Bright's disease. It is of little use to clear up the collæmia if the nutrition of the heart is so bad that it could not keep up a proper circulation, even with no collæmia; and circulation being so bad, the fluid is not run off by the kidneys, and the tissues of the body are like a marsh with great stagnant pools in the serous cavities. The water and the collæmia between them now quickly extinguish the flickering flame of combustion.

If this is the common and final ending of ordinary Bright's disease, and if collæmia will produce more and more severe results

in proportion as it supervenes upon an otherwise more and more defective circulation, it follows that a collæmia which would not of itself suffice to produce Bright's disease may yet produce it if it chances to supervene upon either a condition of weakness or debility of the cardiac muscle, or, on the other hand, on a mechanical condition which more or less seriously obstructs the general circulation.

I think, therefore, that it is extremely probable that some people suffer from Bright's disease not because they have more severe collæmia than those who do not suffer, but because they have rather weaker hearts or more obstructed circulation, which allows the collæmia to do greater damage to nutrition and combustion than it would in an individual with a normal circulation; and thus acute Bright's disease may be not infrequently the result of collæmia with acute heart failure.

Now one special condition I have in my mind's eye in making these remarks is that of pregnancy, for here we have, especially in primiparæ, a condition affecting the pressure relations in the abdomen, affecting the work of the diaphragm, the circulation in the great digestive viscera and the abdominal vessels, playing, in fact, exactly the part of the ascites in the case of Edgar G.

And I find in Fagge's "Medicine," second edition, vol. ii., p. 624, the statement: "In women pregnancy is often the cause [of Bright's disease], as the late Dr. Lever showed many years ago, especially in primiparæ, and above all when there are twins."

The bearing of primiparæ and of twins on the pressure relations of the abdomen are too obvious to need further remark, and it is also clear, as it follows from my first principles, that pregnancy is an enormous stimulus, especially in young women and primiparæ, to the nitrogenous metabolism of the system, and this means both excessive formation and excessive retention of uric acid in the body, that is, provision of the material for a more or less severe collæmia in the future. We already know from the relationship of pregnancy to headache, epilepsy, mental depression, Raynaud's disease, &c., as treated of in previous chapters, that normal pregnancy is accompanied by retention of uric acid, and its clearance out of the blood.

But if the pregnancy is not normal, if there is dyspepsia, and still more if there is vomiting, it follows that the blood will become again a good solvent of uric acid, and then some of the large formation of uric acid, or some that has been already retained before the vomiting began, will pass into solution in the blood and a more or less severe collæmia will result. Now vomiting is exactly one

of those things which, I believe, may thus precipitate Bright's disease on pregnancy. And the following case will illustrate several of these points :—

Ellen G., aged 24, admitted into the Metropolitan Hospital on October 12, 1895, being then in the fourth month of her first pregnancy.

Her history showed that on September 28 hæmaturia had been noticed.

On October 1 she had several "fainting fits."

On October 6, suffered from pain in the left side.

On October 8, suffered from vomiting, which continued up to admission.

There was some anasarca and œdema of legs; pulse 68; temperature 98° F. to 100° F., irregular; heart's apex outside left nipple line; abdomen slightly distended; uterus easily felt in hypogastrium; urine, 1014, alkaline, blood-stained.

Albumin (Esbach)...	·4 per cent.	or nearly 1 to 2.
Urea	·9 „	

Left radial artery measured with the arteriometer, 1·9 mm.

Put on iodide of mercury in small doses.

October 19.—Pulse 72; left radial measures 1·7 mm.

October 23.—Pulse 72; albumin to urea 1—4 in place of 1—2 as on admission.

October 24.—Iodide of mercury in full doses.

October 25.—Pulse 84; left radial 1·5 mm.

October 30.—Pulse 96; left radial 1·3 mm.

November 8.—Heart's dulness has diminished and apex come into left nipple line.

November 16.—Pulse 92; left radial 1·5 mm. There is some increased heart dulness, apex has gone again a little to the left and there is some increased œdema of the legs. Some digitalis given.

November 19.—Same condition; pulse 88; left radial measures 1·6 mm. Iodide of mercury further increased.

November 23.—Pulse 85; left radial 1·0.

November 30.—Pulse 72; left radial 1·0.

December 6.—Pulse 88; left radial 1.1. There is still considerable œdema of the legs.

I now came to the conclusion that the iodide had twice cleared up the collæmia and freed the capillaries on October 30 and November 23, but on neither occasion had this been followed by diuresis and removal of fluid, and similarly combustion remained defective and albuminuria profuse.

The inference seemed to be that the increasing abdominal pressure and the increased work that pregnancy, now in the sixth month, was throwing on the heart, prevented it reacting to the removal of the collæmia. I therefore gave up the attempt to do anything with drugs and trusted to nature, with uric-acid-free diet and rest.

If we could have cleared out the abdomen the heart would have recovered somewhat and become equal to its ordinary work, and then the iodide of mercury would have improved the combustion and reduced the albumin to a trace; and the question of terminating the pregnancy was carefully considered with my colleague, Dr. Gow, but put on one side as being on the whole more dangerous than trusting to nature.

I could not but feel, however, that while we were thus waiting, the kidneys and great metabolic tissues were suffering serious damage, how serious it was difficult to say, but I knew from previous experience that such cases kept carefully on milk often got over parturition well, and that Bright's disease then subsided to a greater extent than might have been expected.

Accordingly she was now watched for some months, during which the conditions remained as before, the pulse ran about 80, and the radial artery measured from 1·7 to 1·9 mm. Urine scanty, loaded with albumin and a little blood.

In February, 1896, after reading the most interesting lectures of Dr. Handfield Jones, "The Heart in its relation to Pregnancy, Parturition, and the Puerperal State" (*Lancet*, 1896, vol. i.), to which I shall have to refer again, I made a further careful examination of the heart, and came to the conclusion that the quick pulse rate with a long and indistinct first sound, and a loud second sound both at apex and base, with increased dulness and apex displacement to the left, meant some heart failure before collæmia and the increased work and pressure in the abdomen, and I accordingly put her on a mixture containing phosphoric acid and strychnia, and it appeared to do some good, for the pulse on February 25 had fallen to 72 and the left radial diameter to 1·6 mm., and the urine had increased somewhat to 46 oz. per day, but still there was as before no important result as regards the removal of anasarca and improvement of combustion.

On March 14 I examined the blood and found—

Hæmoglobin	...	33 per cent.	= Blood decimal ·47
Cells	... ...	70 „	

a very dilute and watery blood, owing to the great retention of fluids in the body.

And so things went on without any material change up to April 21, when she was delivered of a full-time living child after a fairly normal labour, and the fœtal heart had been heard and watched for several months past.

The temperature was slightly raised after parturition, and the urine began at once to increase, reaching 113 oz. on the day after it.

April 24.—Urine 80 oz. General anasarca and œdema of legs decidedly less.

May 13.—Temperature now becoming normal after uterine inflammatory troubles, but the patient is weak after them.

Pulse 80 to 90; left radial diameter 1·0 mm., albumin only ·05 per cent. now.

May 23.—Being now again under my care she was put back on the mixture of phosphoric acid and strychnia, and the pulse improved and slowed somewhat.

She remained weak and anæmic, but she wished to go home, and was allowed to do so, continuing the mixture and the uric-acid-free diet.

July 16.—Saw her again; there is still considerable albumin, but she does not wish to come in for treatment with the iodide of mercury.

Her uterine troubles were unfortunate, for, though no doubt the fever helped to clear up the collæmia, appetite and digestion were much upset by them, hence nutrition and combustion remained poor, and the heart did not gain in strength as it otherwise might have.

This case may be summed up as follows:—

(1) Early months of first pregnancy, stimulated nutrition, retention of uric acid.

(2) Some upset or abdominal pain causing nausea and dyspepsia.

(3) Severe collæmia causing high blood pressure.

(4) Heart failure before the high blood pressure with "fainting fits," this causing, with the collæmia, albuminuria and hæmaturia, in fact, acute Bright's disease.

(5) Vomiting, either with the "fainting fits," a symptom of uræmia, or an exaggeration of the previous nausea and dyspepsia.

(6) Continuation of collæmia, high blood pressure and defective combustion, the latter being increased by the heart failure, which again was intensified by the increasing work and increasing abdominal pressure of advancing pregnancy.

(7) Collæmia partly cleared up by drugs; but the heart is still too much hampered to respond with a free capillary circulation, and so combustion remains defective, and albuminuria continues.

(8) Great relief to heart and circulation at termination of pregnancy, but unfortunately digestion and nutrition are still held down, and so, though the water increases and the albumin diminishes, the heart remains weak and nutrition and combustion defective.

(9) Result. Prolonged cardiac weakness, debility, collæmia and anæmia, prolonged defective combustion and permanent damage to kidneys and great metabolic tissues.

Prognosis very bad for future pregnancies, unless the heart and tissues are allowed a long time to recover; and doubtful or bad as regards the continuance of life.

It has often been remarked that a woman may suffer severely in her first pregnancy, but if she gets over it well she may suffer little, if at all, in subsequent pregnancies, and this is due partly to the fact that the abdominal walls are now lax, and the pressure and derangement of the abdominal circulation in subsequent pregnancies are consequently less than in the first pregnancy; but it is also partly due to the important fact that the heart has had time to hypertrophy and get level with the increased work, and so in subsequent pregnancies the defective combustion is never so severe (even if the collæmia is the same) as in the first pregnancy; and Dr. Jones (previous reference) tells us that in women who have had many children the heart remains permanently hypertrophied.

I was greatly interested and instructed by reading these lectures while this case was under my care, as he points out that normal pregnancy causes hypertrophy of the left ventricle and enlargement of the whole heart; and also that some cardiac failure from defect of this hypertrophy is by no means an uncommon cause of the signs of heart weakness in pregnancy.

He also points out the effects of the abdominal pressure of pregnancy in increasing the work of the heart, and shows that similar heart failure may be produced by abdominal tumours. He further suggests that a previous pericarditis may in some cases explain the failure of the heart to get level with its work in pregnancy.

He points out that the heart may not only fail during pregnancy, but it also fails, perhaps more often does so, in the week after labour; and we must not here lose sight of the existence of post-puerperal collæmia and its possible effects on the heart and circulation.

Dr. Jones points out that this is by some believed to be due to some fatty degeneration of the heart muscle taking place towards the end of pregnancy; but I cannot help thinking that this is a bit

of doubtful physiology and pathology, and that the large excretion of uric acid (which is certain to follow the termination of a normal pregnancy, fed on ordinary meat food—post-puerperal collæmia) which as we have seen probably accounts for the greatly increased danger of giving chloroform at this time (see chapter viii.), also accounts for the frequency of heart failure apart from chloroform, and one of Dr. Jones's cases of death after delivery resembles in its symptoms post-chloroformal syncope.

The drugs that Dr. Jones finds useful in these cases are iron, strychnia, digitalis and nitrite of amyl.

One practical conclusion from these facts and observations would be that all women who have the least sign of cardiac defect or debility should be kept throughout pregnancy on a uric-acid-free diet, to prevent as far as possible the addition of collæmia to these other heart difficulties, either during or at the end of pregnancy.

It would be better still if they could live on the diet for several years beforehand, and of course there must in any case be no diminution of albumin.

Indeed, I think that all pregnant women might with advantage be kept on such diet, for even if by means of digitalis, strychnia, &c., you can prevent the heart from failing, that does not in presence of collæmia make combustion good, and, as shown by the very high arteriometer measurements in the case of Mrs. G., the arterial system is subjected to great pressure and strain.

There is not the least doubt that pregnant women can live on a uric-acid-free diet, for I have conducted not a few of them safely through it on an almost absolute milk diet, and we see by the quotations already given in chapters vii. and viii. that they can often do so with enormous advantage and relief from the very circulation troubles, high blood pressure, and general congestion of which I was speaking; even if we may not throw in a greatly diminished chance of acute Bright's disease, and this last consideration would specially mark the value of such diet in primiparæ.

I have had enthusiastic reports from some of my patients who have passed through these conditions while living on the uric-acid-free diet. The explanation of course is that a diminution in the quantity of uric acid in the blood stream must have a marked effect in diminishing congestion and pain.

I subjoin one as typical from the husband of a patient: "She feels she has much to thank the diet for—few discomforts during pregnancy, easy labour considering the child's size (10½ lb.), quick recovery, and a good milk supply. And this in the case of one

whose mother, grandmother and aunts (all meat fed) failed to suckle their childre n."

Of course, those do best who have lived all their lives on a correct diet, or have at least been on it for several years before the strain of pregnancy is encountered.

I would suggest also, while these cases are fresh in our minds, that heart failure, in other conditions than those met with in pregnant women, may allow of the production of seriously defective combustion (Bright's disease) by a collæmia that would not by itself have sufficed to produce it, and that in fact heart failure is an important contributing cause of such failure of combustion ; the bad prognosis of heart failure in Bright's disease is well known, but this heart failure may have actually preceded the defective combustion, and been one of its causes. Hence the relation of Bright's disease to fevers may be a double one, first to the post-febrile collæmia already mentioned, and second to the weakened and debilitated heart muscle which so many fevers also leave behind them.

If the collæmia is slight and the heart strong there will be merely a temporary bradycardia with subnormal temperature as the sign of defective combustion ; but if the collæmia is severe, and especially if the heart muscle is also weak, we shall have more decided and prolonged interference with combustion, shown not only in subnormal temperature with a quick and often irregular pulse, but with varying degrees of albuminuria and diminished urea up to what we have been accustomed to call undoubted Bright's disease ; so that every post-febrile and collæmic bradycardia is Bright's disease in epitome, and differs from it merely in degree. Thus acute Bright's disease may be not only acute collæmia, but acute collæmia with its combustion effects intensified by a weak heart ; and this weak heart will be either capable of improved nutrition and better work or not capable of these. If it is not capable the case goes to the bad, as there is no possible means of stopping the defective combustion, and, as we have seen above, removing the collæmia may not be sufficient.

If, on the other hand, the heart has been only temporarily disabled, and, with the removal of the mechanical cause of such disablement, can attain to improved nutrition and power, combustion will improve somewhat, even in spite of the collæmia, and with improving combustion the collæmia itself will be diminished or cleared away ; hence we shall get less defective combustion extending over a longer time (chronic Bright's disease).

But here again, also, there eventually comes a time when the

nutrition of the heart muscle is so bad that satisfactory circulation and combustion are no longer possible, and then collæmia and hydræmia finally put out the fires.

We have here standing out clearly the two conditions which in any given case of Bright's disease may render it impossible to cure by means of the iodide of mercury: (1) the possible evil effects of the drugs themselves on digestion and nutrition, which more or less prevent their putting an end to the collmæia, and (2) heart failure.

I will now give notes of two cases of Bright's disease in which the instruments for measuring capillary reflux and blood pressure were used:—

The first case may be said to illustrate what not to do, and the second case what to do, and they show that mere staying in bed does not of itself either lower blood pressure, improve combustion or diminish albumin.

Mary W., aged 25, admitted into the Royal Hospital on October 23, 1899, with Bright's disease and some œdema of legs. Urine 1020, albumin 1·5 per 1,000 (Esbach).

October 26.—Temperature 98° F. both morning and evening. Pulse, 80. Capillary reflux 9–10, decidedly slow. Blood pressure 160. Usual heart signs of high blood pressure. Put on mist. pot. cit. gr. xxx. ter.

October 27.—Mist. given 4^{is} horis. Diet contains fish and calves' foot jelly. Weight, 7 st. 1 lb. 8 oz.

October 30.—Temperature becoming more subnormal. Pulse 72. Blood pressure 150.

November 2.—Urine keeps alkaline most of the day, no alteration in amount of albumin. Pulse 96. Blood pressure 170. Weight 7 st. 4 lb., this is not due to increase of œdema of the legs, as it has not increased.

November 6.—Urine still occasionally acid. Given some potatoes. Pulse 72. Blood pressure 170—180.

November 9.—Blood pressure 150—160. Weight 7 st. 7 lb.

November 13.—Blood pressure 150—160. Still no change in the amount of albumin. Citrate of potash left off.

November 16.—Pulse 100. Blood pressure 150. Capillary reflux 8. Temperature subnormal. Albumin has increased to 2·8 per 1,000. Weight 7 st. 13 lb.

November 20.—Pulse 96. Blood pressure 160. Capillary reflux 7—8. No drugs since 13th. Given pot. iod. gr. viii. Tinct. nucis vom. ♏ iv. ter

November 23.—Pulse 108. Blood pressure 140—150. Albumin from 2·0 to 2·5 per 1,000. Weight 7 st. 10 lb.

November 28.—Pulse 108. Blood pressure 130—140. Capillary reflux 7—8. Mist. 6^{is} horis.

November 30.—Pulse 108. Blood pressure 150—160. Albumin 3 per 1,000. Weight 7 st. 12 lb. Put on uric-acid-free diet, milk and cheese, no tea. She likes fish and calves' foot jelly better.

December 4.—Pulse 120. Blood pressure 160—170. Given also pil. hyd. gr. ii. n. et m.

December 7.—Pulse 120. Blood pressure 160—170. Albumin from 2·0—2·7 per 1,000. Does not like uric-acid-free diet. Put back on fish, custard and eggs.

December 11.—Pulse 110. Blood pressure as before. Albumin 2·25 per 1,000.

December 14.—Pulse 112. Blood pressure 160. Sodii chlor. gr. xx. added to mixture. Weight 7 st. 10 lb.

December 18.—Pulse 100. Blood pressure 150—160. Albumin as before.

December 21.—Blood pressure 150—160. Temperature 97° F.—98° F. Urine 41 oz. Albumin 2·5 per 1,000.

As the patient was unable to alter diet, and as there thus seemed little chance of improvement, she was allowed to go home.

The case is interesting as showing that citrate of potash neither lowered the blood pressure nor diminished the albumin; it was not the treatment I should have chosen, but she had already been on it and so I continued it.

I think also that citrate of potash would have done better than this, if urates had not been constantly poured in day after day in fish and calves' foot jelly.

A point of some interest is the fact that with this subnormal temperature, defective capillary circulation, and constant excretion of unmetabolised albumin, she steadily gained in weight to the extent of 10½ lb.; this was a real gain in weight, probably a laying on of fat, which, like the albumin, had escaped combustion, thus illustrating the relationship between high blood pressure, defective capillary circulation and obesity. Later, when on iodide and mercury, which promote combustion, she lost 2 lb.

With regard to obesity, I find that it is constantly associated with slow capillary reflux and high blood pressure (hence, no doubt, the association in the popular mind between stoutness and apoplexy), and I have no doubt that it is merely one more result of defective combustion and, like the other results, can be controlled by controlling the circulation.

In the above case also it may be noted that even the iodide and the mercury, when we put her on to them, made but little headway against the collæmia, which had been increased by the alkali and the heart failure, as shown by her quickened pulse. The heart failure occurring as we see in spite (? because) of feeding upon fish and calves' foot jelly, and a similar feeding up produced equally disastrous results in the case of Edgar G., previously recorded; and I was practically unable to alter this wrong diet, introducing fresh poison.

And now we shall see different drugs, a different diet, and a very different result.

Timothy C., aged 35, admitted into the Metropolitan Hospital December 1, 1899.

Four weeks ago he got wet through and worked on in his wet clothes. A week later he suffered from headache, dyspnœa, and loss of appetite. One week ago face and ankles noticed to be swelling.

The sequence here was clearly (1) retention by cold and wet followed by (2) the collæmia of the rebound, causing, among other things, headache. This caused (3) depression of metabolism and a general rush of all his stored urates into the blood. This caused more severe and chronic collæmia, which resulted in (4) heart failure and dropsy—the complete picture of Bright's disease; (2) represents the migraine or pre-albuminuric stage, and the correct use of a precipitant drug at that time would have saved him all the rest. On admission the headache was severe, and there were signs that uræmia was close at hand.

December 2.—Pulse 52. Capillary reflux 8. Blood pressure 180—190. Heart's apex just inside the left nipple line. First sound long or reduplicated; second sound very loud.

Urine 1020; albumin 7·5 per 1,000 (Esbach).

He was given a bread and milk diet and a mixture containing am. brom. gr. viii., sodii iodidi gr. viii., sodii chloridi gr. xv., t.i.d., and a calomel purge.

December 4.—Headache still very bad; some vomiting and retching. Takes very little food. Some phenacetin given, which relieves head for a time. Temperature about 97° F.

December 6.—Headache less, swelling of face also less. Still no appetite, and slight nausea. Temperature 98° F. to 99° F. Pulse 72; capillary reflux 7—8; blood pressure 160—170; albumin 2·5 per 1,000. Given pil. hyd. gr. i. n. et m., fruit and cheese added to diet. Fluids limited to 1½ or 2 pints, provided this can be done without hardship. I have here followed the practice of von Noorden (*Inter-*

nat. Med. Mag., May, 1899), for though diminished fluid will increase the relative amount of uric acid and collæmia in the blood, just as it increases the relative number of red cells, still it must undoubtedly relieve the work the heart has to do, and if it allows the heart to contract and prevents its dilating, it saves us from that worst of all failures of combustion which occurs when collæmia is complicated by heart failure, a condition which, in Bright's disease and all other failures of combustion, is simply hopeless. The central engine is broken or defective, and it is no longer possible to keep up a satisfactory capillary circulation even if there is no collæmia; still less is it possible with constant and severe collæmia, as in Bright's disease.

December 9.—Better and more cheerful; he was dull and lethargic before. Has wrinkles round his eyes. Headache slight; no nausea. Weight, 10 st. 3 lb. 10 oz.; pulse 70; blood pressure 160—170; albumin 1·5 per 1,000. Pil. hyd. increased to gr. ii. at night.

December 13.—No headache for two days. Temperature has risen and is now fairly steady about 98·6° F. Pulse 78; capillary reflux 6; blood pressure 130—140; albumin 1·2 per 1,000.

I do not mention the quantities of urine because owing to the limitation of fluids the usual increase of water did not show. The withholding of fluid no doubt hastened the clearing of his tissues from œdema, as the blood more quickly took up what it required from them; hence metabolism gained by removal of œdema quite as much as it lost from the relative increase of collæmic granules.

December 16.—No headache; much better. Weight 10 st. 1 lb. 4 oz.; pulse 80; capillary reflux 5—6; blood pressure 120—130; albumin 1·0 per 1,000.

December 20.—Pulse 84; capillary reflux 5; blood pressure 120; albumin 0·5 per 1,000. Is tired of cheese, so was given some cheese dishes and milk puddings for a change.

December 23.—Weight 10 st. 1 lb.; albumin 0·5 per 1,000, or only a trace. Pulse 80; capillary reflux and blood pressure as before.

December 29.—Had some turkey on the 25th and was no worse. Albumin too little to be estimated. Temperature very steady for some time past, about 99·0° F. morning and evening, sign of good and complete combustion; and with this good and complete combustion a grain of uric acid in a morsel of turkey and plum pudding had no effect at all. Had combustion been less good it might have had an effect, or if we had fed him with 6—8 gr. of uric acid every day

we might have found it impossible to get up this good combustion and been driven back, more or less, in spite of our retentive drugs.

Pulse 88; capillary reflux 5; blood pressure 120. Weight 10 st.

January 6.—Is now up and about. Pulse 100; blood pressure 110—120; capillary reflux 5. Temperature steady at 99·0° F. Will continue diet and the mixture, but may leave off the pills. Combustion is now so good (albumin a trace only) that the mixture alone will suffice to keep it going if there is no fresh introduction of poison.

This, of course, is rather a large "if," especially in dealing with uneducated people. This man does not like the diet much, but still has done his best to help us in keeping to it, and I have done my best to impress upon him that his life depends on his continuing it, and I believe he will at least make an effort to do so.

In twelve months' time, or possibly sooner, he will have splendid blood, good capillary circulation and combustion, no albumin, and normal blood pressure; and no one will ever guess that he has had acute Bright's disease and been within an inch of uræmia and destruction.

An interesting point is, What becomes of the urate in these cases? We have put an end to collæmia and produced good combustion by drugs that cleared the blood of uric acid and produced retention. What becomes of the urate thus retained?

For some months we have to keep on the retentive drugs, or it would come back into the blood in force and overwhelm us; but the effect of a uric-acid-free diet is to increase the solvent powers of the blood for uric acid, and I believe the stores are slowly washed out, passing thus through the blood and kidneys in small quantity and good solution, that is, in a condition to do but little harm; and by the end of twelve to eighteen months (just as occurs in the case of the uric acid headache on diet) those stores and accumulations have practically ceased to exist, and health is absolute, complete, and free from danger except by a relapse in diet.

We may note in the above successful case there was a steady loss of weight, which probably was not all loss of water but some combustion of fat, just as in the unsuccessful case there was a large gain in weight, probably largely made up of uncombusted fat.

We may note how, as the capillary reflux quickened and the blood pressure fell, the albumin steadily diminished; in the other case the capillary reflux did not quicken, combustion did not improve, and albumin did not diminish.

In both cases the heart quickened, but in the woman's case this was

due to heart failure before high pressure; in the man's case it was an illustration of Marey's law, the pulse quickened as the pressure fell, and a pulse of 80—88 corresponds to a temperature of 99° F.

Perhaps in this case we overdid the combustion; the pulse was a little too quick and the temperature a little too high. I should rather be inclined to say that our so-called normal is a little too low, and that in those entirely free from uric acid a higher normal would obtain, for the capillary reflux of the meat eater is always slower than that of the man who abstains, and every slowing of capillary reflux means defective combustion and subnormal temperature to a corresponding extent.

No doubt our daily fluctuations of surface temperature, down in the morning and up in the evening, are the work of uric acid and its effects on circulation and combustion; and this accounts for a fact I have often noted, that the salicylates reverse the normal temperature curves, making them high in the morning and low in the evening, just as they reverse the circulation curves, making the capillary reflux quicker in the morning and slower in the evening.

And this is due to the fact that salicylates are better solvents of uric acid in the acid tide of the night and worse solvents of it in the alkaline tide of the morning; hence there is more uric acid in the blood, slower capillary reflux, and lower surface temperature at night under these drugs. And anyone who will give salicylates on a normal temperature with its morning fall and evening rise, will probably find, especially during the first two or three days on the drug, when there is most uric acid for it to act upon, that he has now a morning rise and an evening fall, just reversing ordinary curves; and the circulation curves, and no doubt also nutrition and combustion, are similarly altered, and then the largest rise of urea will be after breakfast and the smallest after dinner (see previous remarks on fig. 3).

Temperature, like capillary reflux, blood pressure, and granules, is here, as elsewhere, the index of the quantity of uric acid in the blood.

The above cases also illustrate another point of interest, and show us the value of the measurement of the capillary reflux. In Mary W. slow capillary reflux, with quickening pulse, and blood pressure falling, means heart failure. In Timothy C. quickening capillary reflux with quickening pulse and falling blood pressure means improving combustion, in fact fever in epitome; and the power of distinguishing the one condition from the other is of great importance.

We can see pretty clearly the main points in the pathology and treatment of Bright's disease. It is but a name for the defective combustion of albuminous tissues and foods which defective circulation produces. And the cause of the defective circulation is uric acid present in colloid form obstructing the capillaries.

Similar defective combustion similarly produced will affect either albumins (albuminuria), sugar (glycosuria), fat (obesity), sulphur (sulfituria or cystinuria), or other constituents of the blood and tissues.

The defective combustion is at first functional, and with the removal of the cause soon comes to an end, as in the case last recorded.

But after it has continued some time it produces atrophy of tissue, as shown, for instance, by Semmola in the case of the skin, and then combustion must remain defective.

Within the limits imposed by this pathology we, having power over uric acid, have also power over circulation and combustion.

This pathology suffices to explain the relationship of Bright's disease to all other diseases, and also to diet, exercise, clothing and climate.

Migraine with its slow high tension pulse, its low surface temperature, its falling urea, its increasing albuminuria, differs from Bright's disease in degree only; prolong it over days in place of hours and you have the full length picture of Bright's disease, and, as we have seen, the one only too often passes into the other.

Then, also, the treatment of the one is the treatment of the other; clear the blood of uric acid and free the capillaries and you have cured either

The treatment of migraine is to clear the blood of uric acid and so order the diet as not to be continually introducing into the body an excess of it, and nothing more need be done for Bright's disease.

Any drug that clears the blood of uric acid will do what is required, but if it fails to clear the blood it will be useless, and we have therefore to consider which drug is most likely to succeed under the conditions present in a given case.

The drugs I have used may not be the best—some other metal, for instance, may have more power than mercury; and we want a clear understanding of their mode of action and not a mere blind following of a given prescription.

The pre-albuminuric stage of Mahomed is simply migraine and the functional troubles that accompany it, the headache being more or less marked according to the development of the anatomical factor

(see chapter vi.). And the transition from this to Bright's disease is but the development of migraine into morbus Brightii, which can be seen almost every day.

The fall of urea at the onset of Bright's disease, upon which Semmola lays so much stress, is, like the corresponding fall in fatigue, in migraine or any temporary collæmia, a measure of the defective combustion which collæmia and obstructed capillaries produce.

If we succeed in removing collæmia we shall see a corresponding rise of urea, just as occurs naturally the day after fatigue (figs. 46 and 47), or in Bright's disease, as shown in the case of Lily T., above given, and the same drugs will also prevent fatigue and the fall of urea that accompanies it (fig. 48).

The fact that the amount of albumin in the urine is absolutely proportional to the defective combustion, but in no way dependent upon the kidney lesion, accounts for the points so ably insisted upon by Semmola, and also for the fact that by controlling combustion we can reduce the albumin to a trace in a week, while the kidney lesion, even if capable of repair at all, must obviously take a longer time.

And the effect we thus produce in pathology has its absolute counterpart in physiology, as we are there able to control the formation and excretion of urea from day to day and hour to hour by controlling the uric acid.

In migraine with albuminuria, which comes between the two, we can prevent all trouble by a diet which prevents excess of uric acid from finding its way into the blood.

The relationship of Bright's disease to acute fevers is simply its relation to the defective combustion of post-febrile collæmia, often associated with some cardiac debility; every fever causes retention of uric acid, as we saw demonstrated in a most interesting manner in the case of measles previously narrated.

At the end of the fever there is a plus excretion of uric acid to a corresponding amount, producing, as it passes through the blood, obstructed capillaries and defective combustion to a corresponding extent.

In the case of other acute fevers there is not very rarely a temporary albuminuria on one or two of the days of subnormal temperature that immediately follow it; the subnormal temperature is a sign of deficient combustion, and the albumin when present is but another sign of the same thing.

It follows that the chance of albuminuria and nephritis following scarlet fever depends partly on the quantity of uric acid available for

solution in the blood, and this in turn depends upon the diet before and during the fever.

In this connection it would be of great interest to observe whether vegetarians* have immunity from these sequelæ, and my experience, so far as it goes, is decidedly in favour of this being the case.

The same fact explains also the well-known importance of an absolute milk diet during the course of the fever.

Several years ago I came across an observation made by Professor von Jaksch in an article on kidney diseases in children,† which was of immense interest from my point of view; for after naming a considerable number of drugs as practically useless he goes on to say that only with regard to one drug would he be inclined to make any exception, viz., salicylate of soda, for he has been decidedly impressed with the idea that cases of scarlet fever treated energetically and from the very beginning of the disease with salicyl preparations have not only had their dangers in general diminished, but have that specially dangerous complication, scarlatinal nephritis, banished from their course.

If this observation should prove to be correct it would amount almost to a demonstration of my point, for if uric acid instead of being stored up during the fever is steadily eliminated by the action of salicylates as a solvent, there would obviously be little or none left to get into the blood at the end of the fever to produce collæmia and defective combustion, albuminuria and nephritis.

We have here an important indication for the treatment of many febrile diseases besides scarlet fever, though in all of them it would be a still greater advantage to have been on a uric-acid-free diet for some years before their onset. But life on a uric-acid-free diet might not only banish the sequelæ of a fever, but even do away with the fever itself, though this is difficult to prove except by experience on a very large scale, which is not at present available.

With reference to the value of salicylates in scarlet fever I was interested to see a note by Dr. Dobson Poole on this subject (*British Medical Journal*, 1899, vol. i., p. 1274), in which he said that he had been treating this fever with salicylates "with such promising results as to almost make this into a routine method," and he specially mentions its apparent value in families prone to

* In making this observation it will be necessary to distinguish between vegetarians who eat eggs and pulses and drink tea, and those who are on a uric-acid-free diet (see chapter xvii.).

† *Deutsche medizinische Wochenschrift*, 1888 Nos. 40 and 41.

develop rheumatism or tonsil troubles in the fever; and I wrote a letter which appeared in the same journal, p. 1376, mentioning the above points.

Before leaving these subjects, I must mention a case narrated by Semmola,* because it illustrates several points I want to make clear. A woman, about the climacteric period, goes to see a medical man on account of feeling ill, and having a little skin eruption; he examines her water and finds sugar; he therefore puts her on a diabetic diet, but after some weeks she feels no better and comes to Semmola, who finds that she has now no glycosuria, but an albuminuria in its place, and he thereupon makes the most instructive remark that we are not dealing either with diabetes or with Bright's disease, but with a failure in combustion, *i.e.*, with a failure in the metabolic activity of the liver, skin, &c.; give such a patient excess of sugar, she would have glycosuria, or excess of albuminoids, albuminuria; and I shall mention an exactly parallel case in the next chapter, and for a case in which strict diabetic diet stopped glycosuria but produced albuminuria in a woman, aged 64, see *British Medical Journal*, 1896, vol. ii., p. 1443. From this it follows that we are dealing with diabetes and Bright's disease, for the foundation condition common to both is the defective combustion of collæmia.

The relationship of Bright's disease to diet is simply its relationship to the amount of uric acid formed and introduced into the body by any diet. The more uric acid thus formed and introduced, the more certain is it that at some future time an excess will be present in the blood.

But if a man is killed, say by accident, in the prime of life, before his metabolism has begun to slacken, he may never have excess in his blood at all, for the continual introduction of the stimulant uric acid keeps his blood clear, though it ever accumulates more and more in his body (see chapter v.).

But beyond a certain point this stimulation and accumulation cannot go, for the machine is only wound up for a certain small number of years, even if the gradual accumulation of urates in various organs and tissues does not of itself suffice to clog the wheels and cause diminished efficiency in various functions; and eventually he will have a gradually increasing collæmia, and all the worst results of defective metabolism, including Bright's disease, will make themselves evident, and this defective combustion will

* *Archives de Physiologie*, 1883.

be precipitated or increased if he has also managed in any way to strain or weaken his heart.

But almost the same thing may occur to him earlier in life if he gets an upset, such as fever or a severe accident. The fever causes a fluctuation in uric acid and may also weaken the heart, and the collæmia which follows it may so lower his nutrition that it gets down and is unable to rise, and then all his urate accumulations will come through his blood and further depress combustion and lower nutrition, and he soon finds that he has Bright's disease, obesity, diabetes or other chronic condition of deficient combustion (see chapter iv.).

Such a condition of things is often seen after influenza, but any fever may act in the same way and produce similar results. Hence the best treatment of influenza, as of other fevers, is that by salicylates.

An accident, again, such as a broken leg, especially if it comes near the time of life at which, in any case, nutrition would naturally begin to fail, will serve to precipitate the same state of things.

And this condition of lowered combustion and deficient nutrition is just that in which any microbe that comes past is able to take root and flourish, and the sufferer finds perhaps that phthisis or some other microbic malady has been added to his troubles.

This is probably the way in which some families of children get one disease after another, until they have run through nearly all the exanthemata, each fever leaving behind it a depression of nutrition which predisposes them to take the next.

In a word, Bright's disease is a result of our meat-eating and tea-drinking habits, and as these are common, so also is the disease, and much more common, I believe, than available statistics at all serve to demonstrate.

Everyone who has a capillary reflux constantly slower than 5 or 6 half seconds must have some amount of collæmia, and is on the way to Bright's disease or other form of defective combustion.

Thus exercise when it produces fatigue produces also collæmia and migraine; and migraine, especially if accompanied by albuminuria, is but the first stage of Bright's disease. But the effect of exercise is dependent on diet, *i.e.*, on there being some uric acid available for solution in the blood. On a uric-acid-free diet or one in which milk is the only animal food, exercise cannot produce severe collæmia, and then it will produce relatively little fatigue and no headache or albuminuria; so that it is only when indulged in by those who live on a diet containing much meat and tea that exercise and fatigue do harm (see chapter viii.).

I believe that the albuminuria which exercise may produce is brought about in exactly the same way as the fall of urea and the fatigue which it also produces.

The fall of urea is proof of defective metabolism and combustion, and carry this a little further we get not only deficient formation of urea, but the albumen of the blood will be imperfectly metabolised and begin to diffuse and be passed in the urine; and carry it one step further still, and the blood elements themselves will disintegrate, and we get paroxysmal hæmoglobinuria or its equivalent; and of this the causation is in all cases the same, namely, defective combustion from defective circulation, which again is due to excess of uric acid in the blood, which explains the excess of uric acid found in the urine in these cases.

Speaking of migraine reminds me that fatigue has often been observed to precipitate in the same way the fits of epilepsy.

Clothing affects Bright's disease merely to a slight extent, according as it acts for or against the production of collæmia, *i.e.*, cold from too little clothing acts with collæmia in causing a deficient circulation in the skin, and thereby promotes a deficient metabolism in this important tissue. On the other hand, the warmth and equable temperature of bed act against the uric acid, and tend to keep the skin well supplied with blood, in spite of a certain amount of vascular obstruction by uric acid.

Clothing which is too warm promotes collæmia by increasing the alkalinity of the blood, on the other hand, clothing which is too light will cause retention of uric acid, which will be followed at some future time by collæmia. But when there is not much uric acid in the body to be dissolved and brought into the blood, the chief effect of warm clothing is to keep up the temperature of the skin and thus to antagonise the evil effects of collæmia.

Climate acts in the same way, for cold and damp chill the skin and also cause increased precipitation of colloid uric acid, thus in two ways tending to diminish its nutrition and metabolism. Therefore a cold climate aids uric acid in producing defective function and nutrition and eventual atrophy of the skin, while a warm one tends to prevent these effects; hence Dr. Solly (previous reference, p. 170) is right in recommending a warm dry climate.

Again, a climate in which there are great and sudden fluctuations of temperature is one in which there will be corresponding fluctuations in the excretion of uric acid and in the amount passing through the blood.

A steady elimination keeping pace with formation and introduc-

tion is better; but best of all is the same steady elimination with little or no introduction, so that the body and blood get clear and remain so. Heat is not a depressant for those free from uric acid; but it depresses meat eaters and tea drinkers, because it brings excess of uric acid into their blood, and the power of standing heat without depression and undue fatigue is proof of freedom from uric acid. Those who have stored little uric acid in the cold of winter have little or no depression in the spring. The things, therefore, that lower acidity are useful in antagonising this action of cold, and acidity falls and rises with urea, and the more food the higher the urea; from which it follows that those who would be free from such common troubles as rheumatism in its many forms, gout and catarrh, and probably also from the defective combustions we are specially concerned with in this chapter, must eat less in cold weather, not more as is commonly supposed.

To eat less is to have lower acidity, and cold will then have less power to retain uric acid, to drive it into the fibrous tissues or to store it up in the glands for future collæmia, and a very little auto-experimentation will soon convince sufferers that this is so.

Provided that little food is eaten even some meat and tea may be taken without much harm, as the urate is excreted as introduced; but when we remember that every grain of uric acid that passes through the blood affects its quality, and that urea would have to be kept below physiological levels, the advantages of such a plan are seen to be few.

But those who keep urea below the physiological level to cure arthritis, undoubtedly run some danger from diseases that see their opportunity in failure of nutrition, such as phthisis or carbuncle, so that except for a temporary purpose I do not advise low urea. It is better to feed up to the physiological level and clear out by means of salicylates, or to keep very warm and eat plenty of potatoes, and, best of all, so to feed children that they shall not have a great excess of urates in their bodies requiring to be cleared out.

With regard to atrophy of the skin, so much stress has been laid upon its thinness and wasting in Bright's disease by the late Professor Semmola and others, that it occurred to me that it might be possible to measure the thickness of the skin in the living, and I accordingly went to Mr. Hawksley, and he made an instrument for me which he calls a "dermimeter," by adapting one used by scientific instrument makers for measuring the thickness of microscopic glasses; and with this I have made a few observations which, so far as they go, show a relatively thin skin in Bright's disease. Thus

May P., aged 11 years, in the last stage of Bright's disease (large pale kidney), had a skin measuring $\frac{8}{100}$ millimeter; while Martha V., of the same age, surgical patient, with periostitis and much wasted, had a skin of $\frac{11}{100}$ millimeter, both measured on the back of the hands.

It is obvious that this pathology (which makes Bright's disease a defective combustion throughout the tissues of the body, which combustion is largely influenced by uric acid, and is therefore to some extent within our control) makes the prognosis in this disease not only more definite and distinct, but also more hopeful.

The common pathology of Bright's disease may be said to be collæmia, often precipitated by cold and rendered more severe as to its effects by heart failure. But the collæmia is the great central factor; without it cold cannot make the skin circulation very defective, and the heart is not likely to fail.

When Bright's disease is acute, and when we see it before hopeless structural changes have taken place in the heart and great metabolic tissues, there is only one way in which we may fail to cure, and that is by failing to clear the blood of uric acid; but with the knowledge we have this failure should be exceptional, and therefore the prognosis of the acute disease *when seen early* is fairly good.

As regards treatment, there is only one indication, viz., to clear the blood of uric acid and keep it clear, and beside this one all other indications sink into absolute insignificance.

No doubt it is of some importance to keep the surface warm by means of climate and clothing, and so to neutralise to some extent the evil effects of obstructed capillaries on the nutrition and function of the skin, and heat also directly diminishes collæmia; but uric acid controls the circulation in all the tissues of the body and not in one only, and we must never sacrifice the greater to the less, as was done in the case of Ada P., where the hot air baths given for the good of the skin were allowed to keep the blood flooded with uric acid (see fig. 72), to the detriment of the other tissues and their metabolism.

The drug on which I chiefly rely to clear the blood of uric acid is mercury, and it will have been seen that I have used it for this purpose both in physiology and pathology.

The iodide of mercury also seems to be more powerful than other salts, as we have the combined retentive action of iodine and mercury (see figs 17 and 22).

Given freely, and where it is well taken and does not cause

mercurialism or gastro-intestinal disturbance, it will not very often be found to fail in clearing the blood of uric acid and freeing the capillaries.

When it quickly causes mercurialism, when it causes or increases gastro-intestinal irritation and diarrhœa, it quite fails either to clear the blood of uric acid or to do the least good for the Bright's disease.

I had an instructive case with reference to these points under my care a few years ago, of a man who had been in India and suffered from dysentery, and who came under my care suffering both from chronic dysentery and from chronic Bright's disease (large pale kidney).

I should have no doubt that his Bright's disease (*i.e.*, defective combustion) was the result of the intestinal irritation with the chronic collæmia which it helped to keep up.

I treated the dysentery with astringent injections, and having got it within moderate limits I proceeded to try and treat the Bright's disease, and among other things I used the mist. hydrarg. perchlor. c. pot. iod.

This for about a week appeared to do good ; it lowered his blood pressure, freed his capillaries, and increased his combustion ; but at the end of that time the dysenteric trouble increased, and then the drug soon lost all power over uric acid, the capillaries and the combustion.

When mercury or its iodide fails from these causes, other metals may be tried, but, as I have pointed out, they all, like mercury, cause, or are apt to cause, intestinal irritation and to fail in the same way.

The best thing to do in this case is to treat the gastro-intestinal troubles directly, and when they have been got into a quiet state to give salicylates and acids, as in the case of Charlotte W., or gastro-intestinal trouble should be treated with salicylates and bismuth, and acids given later on.

There is also probably no objection to a little opium for the intestinal troubles so long as it is given with the salicylates, which will prevent its dangerous rebound (see chapters ii. and iii. and fig 35).

I am indebted to my colleague, the late Mr. D. H. Goodsall, for the observation that mercury does not salivate or cause the other troubles of mercurialism so long as iron is given with it, and he gives them together as the perchlorides, or the sulphate of iron with sulphate of magnesia concurrently with the mercury, and so far as my experience goes this is generally true. I see also that a similar combination of the perchlorides of these two metals is recommended

in the work of the late Dr. Fothergill as being useful in syphilis. I have also been told by Mr. W. Goodson, of Stratford, E., that he had known of villagers taking water from the cooling tub of a blacksmith (*i.e.*, a solution of iron) along with mercury, to prevent salivation, which it appeared to do, and he had never seen a case taking this mixture of iron and mercury which got salivation. I have, however, seen it fail; but probably it is more difficult to prevent mercurialism in Bright's disease than in syphilis.

As will be seen in the treatment of the last case I recorded, I now use the iodide in a mixture and the mercury separate as pil. hydrarg., and this plan has some advantages, as each can be graduated separately to meet the peculiarities of a given case; then if the mercury gives trouble the mixture can be continued, or if the mixture gives trouble the mercury can perhaps be continued, or the perchlorides of mercury and iron given as above mentioned. Then the other drugs in my mixture, the bromide and chloride, all act in the same way as the iodide, and all, I think, help each other and make the combined effect more powerful.

In this way one has two strings to one's bow, and the danger of all the retentive drugs failing and of getting a terrific rebound with fatal collæmia and uræmia, as in one of the cases I have mentioned, is much less. The best treatment of skin inflammations and other ill effects from the retentive action of iodides is to give salicylates, which quickly relieve the inflammation and lower the temperature. The trouble caused by a precipitant is relieved by a solvent

Morphine also should be remembered; an injection is most useful in bad cases of uric acid headache, and it may be used in exactly the same way in uræmia. In both cases it should be followed by a short course of salicylate to prevent the possibility of a rebound.

The main point in the old treatment of Bright's disease was the administration of diuretics, which were supposed to flush out the kidney and relieve its irritation; and this was very good treatment, not because the drugs really did good in the way supposed, but because, as I have shown, every drug which causes a diuresis does so by clearing the blood of uric acid and freeing the capillaries, so that the drugs given did not merely free the circulation through the kidney and cause diuresis, but they at the same time freed the capillaries all over the body and thus promoted increased metabolism and combustion in all the great metabolic tissues.

The action of iodide of mercury in diminishing the excretion of uric acid and causing diuresis, and at the same time promoting increased metabolism and combustion, is very well seen in fig. 57.

If we succeed in clearing the blood of uric acid and thus promoting a free metabolism and combustion and keeping them going, we have cured Bright's disease and the blood improves in quality at the same time; if we fail to clear the blood of uric acid we fail to cure, and the same may be said of anæmia and the diseases treated of in the previous chapter, as well as of the conditions considered in chapter viii.; from which also we see that it matters little how we clear the blood of uric acid so long as we do clear it.

But if combustion has been so long defective that atrophy of tissues has taken place it is impossible to cure.

Dropsy hardly needs any special treatment, it is but a result of obstructed capillaries and heart failure (relative or absolute), and if we can free them and strengthen the heart it will disappear; if the heart is strong and its action slow, clearing the blood of uric acid will suffice to remove the dropsy, which is not often very marked under these conditions, but where the heart is weak, failing and acting quickly, it may be necessary to help and strengthen it with strychnia, strophanthus or digitalis at the same time that we free the capillaries.

When ascites is present to any marked extent it will act as a mechanical hindrance to the circulation and will have to be removed by tapping before drugs can be expected to have much effect, but ascites generally comes late in the disease and is a sign of very defective circulation and relatively weak heart; there is therefore all the more reason to treat it promptly.

Diet has in this disease a double importance, for it is not only the means by which we can regulate the introduction and formation of uric acid, and so the quantity available for mischief by getting into the blood, but by limiting animal food to milk only we appear to be able to supply all the albumens required, in a form which, according to Semmola, demands the smallest amount of metabolic activity to render it a suitable constituent of the blood and tissues. The drawback to this treatment is the large amount of fluid, entailing extra work on the heart.

The presence of more or less albuminuric retinitis is no contra-indication to the above treatment; the hæmorrhages and effusions met with in the fundus of the eye in Bright's disease are very clearly vascular phenomena; they coincide with very slow capillary refluxes and high blood pressure, and are, if anything, a special indication for the prompt and efficient treatment of the circulation.

In a case of this kind sent to me from the Eye Department

of the Metropolitan Hospital by my former colleague, Mr. Holmes Spicer, he reported later that the eye conditions had undergone great change and improvement after I had treated the circulation, the blood pressure having been altered from 160 or 170 to nearly normal.

I have also had quite a series of similar cases of retinitis, in which the treatment of the circulation by diet, more or less aided by drugs, has produced very good, often quite unexpectedly good, results.

I have mentioned above the ending of Bright's disease in heart failure, anasarca and ascites; but if the heart does not fail, but, on the contrary, hypertrophies and gets equal to its work, the patient may live for some time; and if the diet is not altered the chances are that the collæmia will continue and increase, and the heart will constantly have to get more and more powerful to cope with it, and the pressure between the powerful heart behind and the obstructed capillaries in front will get greater and greater, and blood pressure will rise higher till the rupture of a vessel in the brain ends the series of vascular changes.

And those who will investigate the matter will perhaps be astonished to find in how large a number of cases of cerebral hæmorrhage the fatal rupture takes place just in those hours of the day in which there is most uric acid in the blood, and in which, consequently (see fig. 38), the collæmic obstruction is greatest and the blood pressure highest.

I have collected a considerable number of such cases from the records in the daily papers, mostly of the deaths of well-known persons, but shall not take up space by giving them here; the matter is so simple that all can now understand how it comes to be so.

When cerebral hæmorrhage merely threatens, the treatment is just the same as for uræmia and other serious conditions already mentioned; but where the hæmorrhage is actually going on and the blood pressure is found to be very high, no time should be lost in bleeding, and bleeding freely. Ten, fifteen, even twenty ounces may make no decided impression on a high blood pressure, and yet such an impression should certainly be made.

Then help your bleeding to keep down the blood pressure by giving the patient neither food nor drink for many hours.

It has been far too much the routine habit, a habit backed neither by sense nor physiology, to feed these patients, just like all other cases of serious illness, every few hours.

But just think for a moment what is the use of letting blood to

lower blood pressure if, as soon as our back is turned, the nurse is permitted to refill the vascular system by pouring in several ounces of fluid every few hours.

Probably all cases that go down with cerebral hæmorrhage have enough food in their bodies to last for days, more likely weeks, and they will not die for want of fluids while the blood pressure is far above normal.

If they die it is from high blood pressure, and this had either produced a fatal lesion before treatment was possible, or it produced one in spite of treatment because it was half-hearted and inefficient.

The most that should be permitted in such cases is a teaspoonful of fruit juice and water, to moisten the tongue now and again; for the rest, starvation for three to five days will do nothing but good, and may just make the difference between life and death.

After that, if there are signs of improvement, keep down the pressure with the drugs mentioned in previous pages, and keep down fluids rigidly, gradually increasing these and the foods to $\frac{1}{10}$ or $\frac{1}{6}$ of an ordinary diet.

Some of these points are mentioned and enforced, with instances of practical experience, by Dr. G. Keith, in his "Plea for a Simpler Life," p. 50, and my knowledge of blood pressure conditions leads me to endorse the teaching of his experiences most strongly.

After the urgent danger has passed, go gradually on to a sparing diet composed entirely of substances that are free from uric acid. A most interesting case showing what may be achieved by such treatment is recorded in Sir T. Watson's "Lectures on Physic," Ed. v., vol. i., p. 512. It is that of a patient who had his first hæmorrhage at the age of 60. On the advice of a friend he became a pythagorean, eating nothing but vegetables and drinking only water and milk. He lost every paralytic symptom and lived in robust and ruddy health, in full possession of his mental faculties, to the age of 93.

Here, as elsewhere, diet has infinitely more power than drugs; it alone controls the cause, the drugs can merely moderate the effects; but drugs may hold the castle for a few hours when nothing else will do so, and then diet may add thirty good years to the patient's life.

Bright's disease is the great central resultant of collæmia and defective combustion; it merges into or underlies nearly all the other troubles of Group B. Its chief symptoms are mere exaggera-

tions of those of migraine, its causation is identical with it; and, most important of all, the early relief of migraine by diet is often the prevention of Bright's disease. Like all other collæmic troubles, it is relieved by precipitants, and the more powerfully they act the more chance they have of making combustion once more effective.

CHAPTER XIV.

Glycosuria and Diabetes Mellitus.

Glycosuria and diabetes mellitus have interested me because they appear to have some relation to uric acid, a relation which, as in the case of headache and mental depression, has been noted by several observers.

While thinking over this relation I was led to try the effects of salicylate of soda (without any knowledge that it had been previously used by others), and the results in many cases (see paper on "The Use of Salicylate of Soda in Diabetes Mellitus and its Connection with Gout," *St. Barthol.'s Hospital Reports*, vol. xxv.) were so remarkable that this seemed to form another link in the chain connecting this disease or disorder of function with uric acid.

Sir A. Garrod says ("Gout and Rheumatic Gout," p. 472): "In the course of practice I have seen several cases in which gouty patients have become affected with saccharine diabetes, or glycosuria," and he narrates the case of a gentleman of 60 who had had gout for twelve years when diabetes suddenly came on, and for more than four years there were no gout attacks. Then the diabetes was checked and the gout soon returned. It is now quite obvious why a precipitation disease should thus alternate with a collæmic one.

The late Sir W. Roberts says ("Urinary and Renal Diseases," Ed. iv., p. 256): "The subjects of obesity and of the gouty diathesis are very prone to a mild form of diabetes," or as we can now put it in one word, failure of combustion.

Professor Latham (*British Medical Journal*, 1886, vol. i., p. 737) has written about a form of diabetes which originates, he believes, in some error in the metabolism of muscular tissue, and he says that in this form of the disease salicylic acid treatment is of the greatest importance, and remarks that these patients often have excess of uric acid in their urine and suffer from neuralgic pains in the joints and limbs.

Then the late Dr. James Anderson, in an extremely interesting

paper in the *Ophthalmic Review* (February-April, 1889), mentions in many places the connection of gout with diabetes, and at p. 18 says: "Many clinical facts go to show that gouty arthritis and diabetes mellitus are in certain cases merely transformed symptoms of the same diathesis, not present at the same time but one taking the place of the other." This, as will be seen, corresponds exactly with my previous quotation from Sir A. Garrod.

Dr. Anderson also makes several interesting quotations from Fagge's "Principles and Practice of Medicine," to the effect that both gout and diabetes are due to disorder of hepatic function.

Now some hyperæmia or congestion of the liver is nearly the only fact in the morbid anatomy of diabetes about which there is any considerable unanimity of opinion among pathologists. Thus, as mentioned by the late Sir W. Roberts (previous reference, pp. 275-276), Sir S. Wilks believes that the liver of diabetes can be distinguished by its appearance (especially its firmness and dark colour) from that of other diseases Dr. Dickinson sees signs of long-continued hyperæmia in the livers of diabetic patients, and Prout observed a gorged condition of veins terminating in the portal system in the same class of patients.

Dr. Saundby, in his lecture on the "Morbid Anatomy of Diabetes," says that the liver is generally enlarged, though he lays special stress on the wasting of the pancreas, and urges its further examination (*Lancet*, 1890, vol. ii., p. 381).

Dr. Pavy again (*British Medical Journal*, 1883, vol. i., pp. 863-866) credits diabetes to a vasomotor paralysis of the chylopoietic circulation, which allows arterial blood to be supplied to the liver in place of venous.

It seems probable also that the various brain and peripheral lesions which sometimes cause glycosuria act by affecting the liver circulation, as Frerichs ("Ueber den Diabetes") points out that puncture of the fourth ventricle only causes glycosuria when the liver contains glycogen.

Now there is evidence that some amount of congestion of the liver is very commonly associated with gout, and speaking of the symptoms of the most common form of gouty dyspepsia, Sir A. Garrod says (*loc. cit.*, pp. 231, 232): "These are generally accompanied with sluggish circulation in the portal system and congested liver"; and he further speaks of fulness and tenderness in the hepatic region as symptoms of this congestion.

The occasional association of glycosuria with ague is, perhaps, an instance of some influence on the circulation of the liver and

spleen causing glycosuria, or of some post-febrile collæmia causing failure of combustion.

We seem, then, to have arrived at this point, that there is a condition of liver congestion which is common in gouty dyspepsia, and bears, no doubt, some relation to uric acid and its presence or absence from the blood.

On the other hand we have glycosuria, in the pathogeny of which congestion of the liver is a very common feature, and this glycosuria has been noticed by several observers to bear a relation to "the uric acid diathesis" and to gout.

Now the relation of glycosuria to gout is, as we have seen, that the one alternates with and replaces the other; where there is glycosuria there is no gout, and *vice versâ*. Now gout corresponds with the precipitation of urate in the joints and its comparative absence from the blood, so that with absence of urate from the blood there is no glycosuria.

But when a gouty patient goes for some time without an attack in his joints, he does so because something has increased the alkalinity of his blood, so that it now takes up instead of depositing urate, and there is collæmia and excessive excretion of urate in the urine; this is the opposite condition to that of gout, and with this there may be (as we have seen) glycosuria.

So that glycosuria corresponds with excess of uric acid in the blood (collæmia), the opposite condition to that of gout.

But congestion of the liver also corresponds to excess of uric acid in the blood, for Sir A. Garrod says (*loc. cit.*, pp. 231, 232): "The more prominent symptoms of the dyspepsia connected with the uric acid diathesis may be thus summed up: heartburn and eructations, oppression, and frequently sleepiness after food; a feeling of distension in the epigastrium, at times accompanied with tenderness; some fulness over the hepatic region, the edge of the liver projecting a little below the ribs, and being occasionally tender to the touch; the tongue much furred, red at the tip and edges, a disagreeable and clammy taste in the mouth, and the saliva and buccal secretion often more adhesive than natural." In two words, there is dyspepsia with its natural result, collæmia, this latter accounting for the oppression, sleepiness, the scanty saliva and clammy taste in the mouth; and in chapter xiii. I have given notes of a case in which marked enlargement of the liver accompanied a uric acid storm, and pointed out that I had myself had very similar experience of the effects of collæmia on the liver.

Now the late Dr. W. M. Ord has pointed out (*British Medical*

Journal, 1889, vol. ii., p. 965) that general high tension may cause an excess of blood in the liver and so glycosuria; and I have shown that arterial tension or blood pressure varies directly with the uric acid that is circulating in the blood, therefore collæmia will cause high tension, and this will produce congestion of the liver and glycosuria.

The causation of glycosuria is thus theoretically complete, and it agrees with the experience of clinical observers that it alternates with gout and corresponds with the absence of gouty arthritis, that is, with the presence of collæmia.

I may say also that my experience agrees absolutely with that of Sir A. Garrod, and that in my own case congestion of the liver always corresponds with collæmia, and to such an extent is this the case that I have come to believe that I can produce some congestion of the liver at pleasure by affecting the uric acid.

If collæmia by hampering the heart and causing back pressure on the venous system does produce congestion of the liver and of the whole chylopoietic circulation, it is easy to see that it may have a causal relation to troubles beyond the liver, such as piles and pruritus ani; and I was much interested to hear from Mr. Maitland Thompson, of Hemel Hempstead, that he had had considerable experience and was prepared to answer for the intimate connection of pruritus ani with meat eating. In several cases reduction of meat had in his experience produced great and permanent relief, but in one case where the patient refused to alter his diet all kinds of treatment, including various surgical measures, had given no relief, and I have myself had many similar experiences.

Similarly there seems to be reason to believe that the enlargement of the prostate which gives so much trouble in men past middle life is often associated with (? caused by) high blood pressure and collæmia, and is greatly relieved by a milk or uric-acid-free diet, which lowers the blood pressure; and Dr. J. Haddon, of Hawick, N.B., has told me that this is certainly his experience of such troubles.

It is interesting to remember that cirrhosis of the liver is sometimes attributed to sclerosis of arterial capillaries (*Gazette des Hôpitaux*, August 4, 1888), and that the late Professor Semmola was in the habit of treating this trouble with milk diet and large doses of iodide of potassium, which would free the capillaries (see *Progrès Médical*, December, 1888, p. 533).

I have now seen many cases in which pruritus ani or vulvæ was distinctly associated with high blood pressure and relieved by its

treatment, and Major Beyts tells me that he has had similar experience. In such cases I have little doubt that collæmia causes congestion of the liver, and that this reacts on the circulation of the organs connected with it, causing piles, pruritus, and various pelvic troubles.

It had occurred to me long ago to enquire, if glycosuria has this causation (*i.e.*, is due to congestion of the liver, which again is due to the general high blood pressure produced by uric acid), ought we not to meet with it in that disease in which high blood pressure is most marked, namely, chronic interstitial nephritis? From my own experience I was not able to answer the question, but on turning to Dr. Ord's paper I was interested to find that he says (previous reference, p. 966): "We not infrequently find that people presenting in a typical form the symptoms of contracting granular kidney have also glycosuria."

Then Dr. Ord narrates a case in which typical angina pectoris coexisted with glycosuria, and it would be impossible to find one more to the point as regards the argument I am here bringing forward (defective combustion of collæmia increased, just as in Bright's disease, by heart failure).

The patient, aged 62, suffered at first, along with his glycosuria, from low spirits and sleeplessness (very marked signs of collæmia). Then he had an attack of quinsy, in which, as is usual during fever, the sugar disappeared, but was replaced by albumin (note the collæmia would also disappear in the fever, and febrile albuminuria is not due to collæmia, and is not associated with excess of diffusible albumens in the blood).

A little later he began to have angina, which afterwards during an attack of gastric catarrh became severe.

Now there is no condition which is more certain to produce collæmia than gastric catarrh (see chapters iv. and x.), and this would account for the increase of the angina, and with this increase of angina there was an increase of the amount of sugar in the urine.

I should explain the sequence of events in this interesting case as follows:—

First, slight collæmia as evidenced by irritability, depression and loss of sleep, this producing general high blood pressure, which, through its effects on a weak heart, produced back pressure and congestion of all behind it; hence congestion of the liver and glycosuria.

Later on the congestion of the liver produced secondary congestion of the stomach and duodenum, and this, acting with some other slight cause, *e.g.*, cold, brought about gastric catarrh.

This last, again, produced nausea and vomiting, which resulted in a fall of urea and acidity; and again, as the result of the fall of acidity, the collæmia became intense; this more and more overtaxed and dilated the heart, the angina increased and became incessant, there was consequently increased congestion of the liver and increased glycosuria, and the patient finally died in an attack of angina.

Dr. Ord is inclined to invoke the nervous system as the cause of the high tension, though he says: "But in a preponderance of the cases presenting glycosuria together with symptoms of angina, the evidence of primary neurotic disturbance has not been so strong."

I have shown that uric acid will obstruct the capillaries and produce high blood pressure, and we had here in action all the causes which will produce collæmia and all the signs of its presence, and I have no doubt that the urine also contains a great excess of uric acid, so that it appears to me to be unnecessary to invoke the action of the nervous system. I do not deny that the nervous system can produce a similar effect, but I assert that in the case in point uric acid alone could and did produce all the symptoms, from the irritability, mental depression and loss of sleep, to the congestion of the liver, glycosuria, the dilatation of the heart and fatal angina.

In an interesting paper on "Angina" ("International Clinics," second series, vol. vi.), Professor T. J. Mays points out that the effects of uric acid on the circulation afford a very complete explanation of several important points in its causation, as it is accompanied by a slow pulse, and is very often worse in the morning hours when there is most uric acid in the blood, and further, like migraine and epilepsy, it may be preceded by feelings of exaltation and well-being (see chapters vi. and vii., and the causation of fatigue and chloroform syncope, chapter viii.).

Two interesting cases in which angina occurred along with gout and diabetes in two fat individuals, are recorded by Ebstein in *Berlin klin. Woch.*, June, 1895, and mentioned in the Epitome of the *British Medical Journal*, 1895, vol. ii., p. 17; in these cases the angina was the result of high blood pressure produced by collæmia, and the diabetes and the fat were the results of the defective combustion it produced.

With regard to high blood pressure, every case of diabetes I have seen has presented its signs to a more or less marked extent, and whether the heart acts quickly or slowly there is always a loud second sound at the aortic base.

In some cases, just as in Bright's disease, there is bradycardia as a sign of the high pressure, but in more cases there is some heart failure with quickened action, though the aortic second sound remains loud and the artery is full between the beats.

But allowing for the debilitating effects of the disease, and the consequent heart failure, the signs of high blood pressure, either actual or virtual, are quite as marked in diabetes as in morbus Brightii, and in fact almost the highest blood pressure I have ever seen was that of a young man who was under my care a year or two ago with diabetes; his radial artery measured 2·2 mm., and his pulse was often below 60; he had probably not been much debilitated by his disease, as it had apparently not existed for more than three or four months.

The capillary reflux is always slow in diabetes, and this is the most reliable sign of defective combustion, as the blood pressure will vary with the strength or weakness of the heart. Then again a retinitis may be met with in diabetes, which is practically indistinguishable from that of Bright's disease (see *Lancet*, 1899, vol. ii., p. 876).

The high blood pressure in the above case led me to put him on the iodide of mercury, which is so useful in the high pressure of Bright's disease, and he did very well on it.

An interesting case is also recorded in the *Lancet* of September 28, 1895, in which thyroid extract administered for myxœdema seemed to make anginal attacks more severe, and what I have said with reference to fig. 30 sufficiently explains this result (see also my letter to the *Lancet* on this point, October 5, 1895).

I have now shown that glycosuria has been observed to alternate with gout, and that this alternation probably means that it is contemporaneous with excess of uric acid in the blood (collæmia), and the signs of this collæmia are practically always present in the circulation.

My thesis also rests on the further facts of which I shall now give details—(1) that acids (which, as I can show, clear the blood of uric acid and prevent collæmia) are useful in glycosuria, and that certain mineral waters containing excess of sulphates, which, like acids, also clear the blood of uric acid, are equally useful in the cure of the disorder; and the whole of these things act like mercury or the iodide of mercury mentioned above; and (2) that salicylates, as observed by myself and others, are very useful both in glycosuria and diabetes, and that they also clear the blood, liver, and other organs of uric acid.

The point about which there seems to be the least room for doubt is that glycosuria alternates with gout, and is commonly contemporaneous with collæmia; and supposing that the collæmia is the cause of the glycosuria there are obviously other ways in which it may bring about this result besides that sketched out above in which it produces congestion of the liver. In this case there is excess of sugar in the blood and glycosuria, because excess of sugar passes from the liver; but supposing that the liver is not thus affected, and that only the normal amount of sugar passes into the blood, it may still come to be in excess in the blood if it is not used up and destroyed in the general circulation; and uric acid, by producing obstruction of the capillaries, may interfere to an important extent with the metabolism of the muscles, skin, &c., and thus bring about glycæmia and glycosuria through deficient destruction of sugar. At this point I think there is an interesting parallel in the pathology of "curare diabetes," in which the excess of sugar in the blood is due to its not being used up in the paralysed muscles (see *Archiv für Anat. u. Physiol.*, 1891, p. 476).

Before leaving these theories I will mention that, as observed by the late Sir W. Roberts ("Urinary and Renal Diseases," p. 255), women suffer less than men after the age of 45; he attributes this relative immunity to the early decline of sexual activity; but I have shown that menstruation, and especially dysmenorrhœa, produce collæmia (see figs. 31 and 32), and a cessation of these disturbances may mean that the blood remains at this period in women moderately free from uric acid for some time; and besides, owing to the previous excretion of some excess of uric acid every month, women, about and for some time after the menopause, will not have so much uric acid in their bodies available for excretion as men of the same age; but I shall have to speak of the effects of menstruation again (see case Mrs. C., further on). With regard to the effects of acids, it is recorded, as I have mentioned before (*Practitioner*, 1891, vol. i., p. 193), that Sir W. Foster, in 1871, gave several patients suffering from diabetes considerable doses of lactic acid, which improved the diabetes, but produced pain and swelling in the joints; and this most valuable record proves several points of importance; first, that diabetes or glycosuria was present in these cases with excess of uric acid in the blood, or the acid would have had nothing to act upon; secondly, the acid acting, as I have shown that it does, in diminishing the alkalinity of the blood and reducing its power of holding uric acid in solution, caused it to be deposited or retained in the joints, where its presence gave

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rise to an arthritis indistinguishable from that of acute rheumatism (see chapter xvi.).

We have here, I think, a strong light thrown upon the causative connections of both rheumatism and diabetes; the condition (rising acidity) which cleared the blood of uric acid produced the one disease while relieving the other; just as mental depression, which is due to collæmia, clears up when an attack of gout is produced. Many observers say that gout alternates with diabetes, and rheumatism does the same, as we see from the above record.

I have also used acids with apparent benefit in some cases of glycosuria under my own care, and I was led to do so by reasoning that they would probably clear the blood of uric acid and have to some extent the same effect as salicylates, and without having any knowledge of Sir W. Foster's cases.

In my paper in *St. Bartholomew's Hospital Reports* (previous reference) I pointed out what has been said about the great effects of certain waters, as those of Contrexéville, Carlsbad and Brides-les-Bains, in curing diabetes, and have suggested that these owe their efficacy to the sulphates they contain; as sulphates, especially sulphate of soda, act the part of acids, interfere with the solubility of uric acid, and clear the blood of it (see *Medico-Chirurgical Trans.*, vol. lxxi.). In the same way these sulphate waters may cure or relieve chronic arthritis by keeping the blood clear of uric acid so that none can be brought to the joints in the blood stream to increase the irritation in them; but if a patient has much uric acid in his blood when he begins to take these waters they may produce an attack of gout, thus clearly showing the way in which they relieve diabetes, by acting like the lactic acid above mentioned—a collæmic disease cured by a precipitant which produces a precipitation disease in its place. In exactly the same way a meat diet relieves some cases of arthritis (gout or rheumatism) by acting as a stimulant and keeping the blood clear of uric acid for a time, and a diet like that of diabetes, which consists so largely of flesh, will have a similar stimulant action and relieve by keeping the blood clear of uric acid for a time, as well as by merely replacing the starches and sugars.

Before I give notes of my cases I may restate shortly a few points about the action of salicylates on uric acid.

A salicylate, then, increases the solubility of uric acid, and must for a time increase the quantity contained in the blood; but though it does this the effects of uric acid in the blood seem to be modified (possibly by its being present as salicyluric acid and in a state of

more complete solution) and it neither affects the capillaries so greatly as uric acid combined with an alkali only, nor does it, as a rule, produce headache.

But though we get salicyluricacidæmia as the first effect of giving a salicylate this does not last very long; the uric acid passes quickly through the kidney and out of the body, and, as I have pointed out, the great excretion of urate under salicylates occurs on the first two or three days of their action, and, after that, excretion falls away almost to the level of formation; thus it comes about that after the first day or two of their action there is not again any great amount of urate in the blood; the capillary reflux then quickens and the blood pressure falls (see fig. 41).

The effects of salicylates, therefore, resemble those of acids and sulphates in that they ultimately clear the blood of uric acid, and they all have this also in common—that they diminish or stop glycosuria or diabetes.

Acids also are commonly used in conditions of slight congestion of the liver; sulphate of soda is supposed to have a special action on the liver, and salicylate of soda again is said to render the bile more fluid and watery; but all of them—acids, sulphates, and salicylates—as we have seen (chapters ii. and iii.), increase the urinary water, and they produce this effect by freeing the capillaries of the kidney from the obstruction produced by uric acid; is it not probable that they produce precisely the same effect on the capillaries of the liver, and for that matter on those of the whole body? Hence, acids and sulphates relieve congestion of the liver by improving the circulation through it, and salicylates render the bile more fluid by the same action, just as they make the urine more copious.

But the salicylates have this great advantage, that they clear the blood of uric acid by removing it from the body; while the acids and sulphates clear the blood (as do also opium, mercury, the iodides, iron, lead and lithia, &c.), by retaining it in the liver, spleen, joints and other tissues.

Prominent among other drugs that have been found useful in diabetes are opium and antipyrin, and they raise the acidity of the urine, and as regards uric acid act the part of acids and clear it out of the blood; therefore all drugs that are useful in diabetes have this effect in common, that they clear the blood of uric acid, and clinical experience and observation go to prove that glycosuria is associated with an excess of uric acid in the blood, and may in some of the ways I have suggested be actually due to such excess; its well-

known relationship to "gout and the uric acid diathesis" being thus susceptible of explanation. And there are two pathological conditions which, having the same action as the drugs just mentioned in clearing the blood of uric acid, also for a time put an end to glycosuria or diabetes. One of these conditions is a fever, and the other is the effect produced on metabolism by a surgical operation. The fact that these conditions do diminish the sugar in diabetes was mentioned at a meeting of the Royal Medical and Chirurgical Society in October, 1892 (see *Lancet* and *British Medical Journal*, October 29), but no explanation was attempted.

After what I have said as to the action of fevers in diminishing the excretion of uric acid in the urine, clearing it out of the blood and diminishing the blood granules, and consequently freeing the capillaries, quickening the capillary reflux and causing diuresis, a soft pulse, and a general increase of metabolism, both in the liver and other tissues; and of the postfebrile rebound which follows their departure, with excessive excretion of uric acid, slow capillary reflux, high tension pulse, scanty urine, subnormal temperature, and diminished metabolism, in all of which points their effects exactly resemble those of opium, mercury, the iodides, and other drugs; I need not do more than point out that, like these drugs, fevers supervening upon a glycosuria or diabetes diminish or stop the excretion of sugar, and the fact is well known and the explanation simple.

I would specially bring to the notice of those who may make clinical observations on the effects of fever on the excretion of uric acid, that the blood and urine are most completely cleared of it during the first few days of the fever, and it is then that the pains resulting from precipitation on joints and other fibrous structures are likely to be met with. In my own person I have several times correctly diagnosed a rise of temperature from pricking and shooting pains in my joints with a diuresis.*

But there may be a considerable amount of uric acid, both in the urine and the blood, as the temperature comes down, even while it is a degree or two above normal; for the solubility of

* Thus the first rise of temperature may run the urine up from, say, 50 cc. an hour to 150 cc. in the same time, and this continues for 3, 4, or 5 hours; but then the supply of water is exhausted, and for the next 24 to 36 hours the blood is concentrated and the urine scanty. The extent and duration of the diuresis obviously depend on the quantity of fluid available, and it is only when there is dropsy, as in the case narrated in chapter xiii., that it can last very long.

uric acid in the blood depends on its alkalinity, and for any given alkalinity the quantity in solution will be greater the more urate there is available for solution.

Now the rapid metabolism at the onset of a fever quickly diminishes the alkalinity of the blood; hence there is at the beginning of a fever considerable storage of uric acid in the body. But, as time goes on, and the patient becomes worn out with the fever and deficient income of food, metabolism will run down in spite of the temperature being still a little raised; the alkalinity of the blood will again increase, and it will take up much uric acid, partly because of its altered reaction, and partly because the stores of uric acid in the body have been increased at the first onset of the fever; hence it often puts an end to the dicrotism of the pulse, as noticed by Marey, Mahomed and others, some little time before the temperature touches normal. But if these facts are not kept in mind, if the uric acid is estimated with sole regard to the fever but no regard to the metabolism, the diminished excretion at the beginning of the fever may be partly balanced by plus excretion near its end, and most contradictory results will be obtained. My results show, for instance, that early in pneumonia there is almost no uric acid in the blood, and yet after death there is more in it than after almost any other disease. We can now see that the fluctuation in one direction is the result of the previous fluctuation in the other.

A fever therefore diminishes the sugar in the urine of diabetes because, by clearing the blood of uric acid and freeing the capillaries, it quickens the metabolism throughout the body, and up goes urea as a result, just as we have seen that it goes up when the blood is cleared of uric acid by any other means; hence the glycosuria diminishes or disappears, especially during the rising temperature of the onset of the fever, because the combustion of sugar is complete. Similarly, when excess of uric acid in the blood diminishes the metabolism throughout the body, urea, as we have seen, goes down (figs. 46 to 49); and for a case in which the febrile state "in some unexplained way" prevented glycosuria, see *Lancet*, 1899, vol. ii., p. 145.

Now the effect of a surgical operation on the metabolism is practically the same as that of a fever. I was much struck with this some years ago, when I chanced to obtain for another investigation the urine of a woman for one or two days before and after the operation of abdominal section. The rise of urea after the operation was enormous, reaching twice or even three times its previous height, and I explained this to myself by supposing that there was

very active metabolism at the seat of operation, and that the patient was thus placed on a highly nitrogenous diet at the expense of her own tissues.

I have unfortunately mislaid the notes of this case, and cannot now give exact figures; but Dr. Young, formerly resident medical officer of the Royal Waterloo Hospital, kindly investigated some cases for me, and I am indebted to him for the following notes:—

E. K., aged 47 ...	June 6 ...	264	gr. urea.
,, ...	,, 7 ...	124	,,
(Plastic operation for ventral hernia.)			
,, ...	June 8 ...	422	,,
,, ...	,, 9 ...	528	,,
,, ...	,, 10 ...	401	,,
,, ...	,, 11 ...	322	,,
Sarah H., aged 49. Ovarian Tumour.			
Before operation		151	gr. urea.
1st day after ,, ...		192	,,
2nd ,, ,, ,, ...		354	,,
3rd ,, ,, ,, ...		188	,,
M. H., aged 56. Ilio-femoral abscess.			
Before operation		232	gr. urea.
1st day after ,, ...		276	,,
2nd ,, ,, ,, ...		452	,,
3rd ,, ,, ,, ...		345	,,

In each of these cases the urea doubled after the operation, the greatest excretion of urea taking place on the second day after it; and for some cases in which the effects of an operation were still more marked see *Lancet*, 1893, vol. i., p. 1413.

Then the acidity of the urine rises with the urea, and urates in the blood and urine vary inversely as the acidity; hence a surgical operation which causes a marked rise in urea will clear the urates out of the blood, free the capillaries and increase the metabolism.

Probably this is the explanation of the curative effect sometimes seen to follow incision in cases of abdominal tubercle; no doubt we get here also, as in other operations, a marked rise of urea and increase of metabolism and combustion, and this is just the effect of the ordinary medical treatment of tubercle by fresh air and excess of food. In the abdominal tubercle we get the increased combustion exactly at the focus of the disease, in the medical treatment we get a general increase of metabolism and combustion. In both cases the result is inimical to the bacilli, it makes matters too hot for them, or burns them up.

I will now give a figure to show the remarkable way in which, in a case of glycosuria, the uric acid and sugar fluctuate together.

The curves are from the case of Rebecca M., aged 45, who was under my care at the Metropolitan Hospital in 1889, suffering from enlargement of the spleen, excess of white cells in the blood, and glycosuria.

I have also pointed out (chapter iii.) that in cases where the spleen is enlarged there is a great excess of uric acid in the urine, and others have pointed out that it is in excess in the blood in these

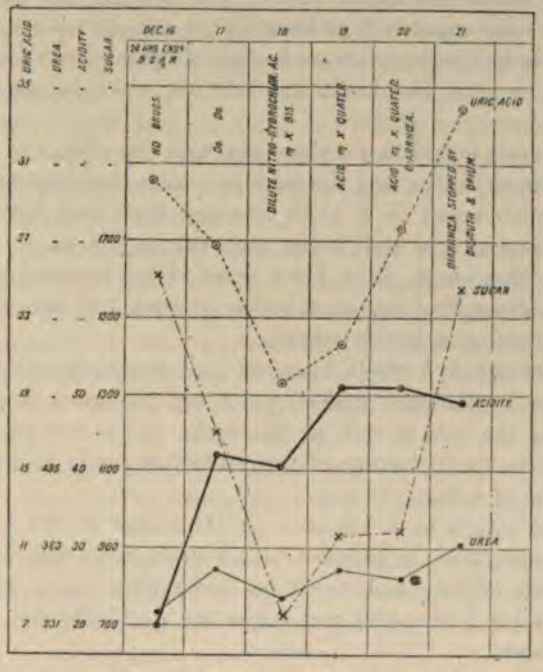

FIG. 61.—CURVES OF EXCRETION OF URIC ACID AND SUGAR IN A CASE OF GLYCOSURIA.

cases; and I notice with interest that Dr. H. A. Hare has published a case of splenic anæmia complicated by diabetes in the *Journal of the American Medical Association*, December, 1899.

It follows that this is just the condition of things in which we should expect to find a glycosuria as the result of the collæmia which is common in such cases.

On December 16 (fig. 61) we see that uric acid and sugar are both hi h, urea and acidity low; on the 17th urea rises a little

and acidity still more, and with this there is a fall of uric acid and a fall of sugar. There must have been some cause depressing the acidity on the 16th, for it rises on the 17th out of proportion to the rise of urea.

Talking of low acidity reminds me of the fact of which we shall see instances among my cases, that patients suffering from diabetes or glycosuria often say that alkalies, such as the bicarbonates of sodium or potassium, do them harm; and we see in this figure the way in which they do it, namely, by increasing the collæmia, and in this figure the uric acid is high because the acidity is low, and the sugar is high because the uric acid is high. So that not only do all drugs, fevers, and surgical operations, which diminish collæmia, do good, but drugs, like alkalies, which increase collæmia, do harm.

I have mentioned in previous chapters the effects of alkalies on metabolism in health, and the way in which they increase uric acid and diminish urea; is it to be doubted that they have the same effect in disease, and that when they reduce the sugar, as there is no doubt they may, they have done it by interfering with the digestion, absorption, and metabolism of food, and have reduced the urea quite as much as the sugar?

And in what I shall have to say presently on the use of salicylates in diabetes, I shall point out the great importance of estimating the urea as well as the sugar, and of not regarding as a curative effect a diminution of sugar which depends on an equivalent diminution of urea.

But to return to our figure; on December 18 the patient took ♏x. of acid. nitro-hydrochlor. dil. twice: urea fell a little and acidity also slightly, and would no doubt have fallen more but for the acid taken; uric acid and sugar fall decidedly and reach their lowest points.

On December 19 she took ♏x. of the dilute acid four times; urea rose a little, acidity more decidedly, as the result of the acid taken; uric acid and sugar both rose a little, though uric acid bears much the same relation to urea that it did on the previous day.

On the 20th the patient again took ♏x. of the acid four times a day; but now she has some diarrhœa, so urea falls a little. Acidity did not rise; uric acid rose, but sugar remained about the same as on the 19th.

This is the only occasion on which uric acid and sugar did not move in the same direction, and I think this is due to there being, on account of the diarrhœa, a lessened absorption of food, and there-

fore a lessened income of sugar (compare previous remarks on the effect of alkalies).

On the 21st the diarrhœa was stopped by means of bismuth and opium mixture, and urea rose; but acidity fell as the result of leaving off the acid and the effect of the diarrhœa on the previous day. Probably the acidity was really low in the early part of this day (21st), and this allowed of the large urate excretion which we see; later in the day, as the result of the opium, it rose sharply, and the balance of the two fluctuations resulted in only a slight fall of acidity in the whole twenty-four hours. I constantly meet with such results in my own experimental work on excretion. And lastly, on this day there is a great rise of sugar, corresponding fairly well with the rise of uric acid.

Taking the whole figure, I think it must be acknowledged that the curves of uric acid and sugar run parallel to each other in a remarkable way, and some of my other cases to be given presently seem to show the same thing.

I here therefore suggest that just as we saw in the previous chapter albuminuria and Bright's disease may originate in a lowering of metabolism, which brings about hetero-albuminæmia, albuminuria and nephritis, so also is glycosuria or diabetes due to similar lowering of metabolism which hinders the final combustion of carbohydrates and, leaving them to circulate in the blood, produces glycæmia.

As I have already pointed out in chapter xiii., one and the same patient may have to-day albuminuria and to-morrow glycosuria, or *vice versâ*.

The lowered metabolism may in each case be due to uric acid, which brings about a deficient capillary circulation in all the great metabolic tissues, its evil effects being no doubt either increased or diminished by concomitant conditions.

We have seen in previous chapters that the quantity of uric acid in the blood controls the formation and excretion of urea, the presence or absence of fatigue under exertion, and probably also the formation as well as the distribution of animal heat; it controls, in a word, the metabolism, nutrition, and function of the whole body, and thus accounts in the most simple manner for a whole series of physiological and pathological sequences.

In this connection there is a most interesting note in the Epitome of the *British Medical Journal*, 1895, vol. i., p. 1, on "Alimentary Glycosuria in Lead Colic." This has reference to an article by Brunelle (*Arch. Gén. de. Méd.*, December, 1894), in which it is

pointed out that the liver is implicated in lead colic because there are modified pigments in the urine, a subicteric tint in the conjunctiva and a diminished excretion of urea. Accordingly, the author gave from 150 to 300 grm. of syrup a day, with the result of producing glycosuria in eleven out of twenty-one cases of lead colic. The glycosuria fluctuated with the colic and generally disappeared with it.

It would be difficult indeed to find an observation more interesting and instructive than that above quoted.

The fall of urea would alone be sufficient to prove that there was severe collæmia present, even if we did not already know that in lead colic there is always a slow high tension pulse and other signs of collæmia (see fig. 13 and remarks on lead colic), and if we did not also know that collæmia is the one certain result of all colic and gastro-intestinal upset. Further, the first action of lead is to clear the blood of uric acid, and the subsequent collæmia is a rebound similar to that following mercury or opium.

In the case of mercury and lead part of the rise of blood pressure may be due to the intestinal irritation (*i.e.*, reflex), but in the case of opium it must be due to the retained uric acid, as there is no intestinal or other irritation, and if the uric acid is cleared out by salicylate it fails to appear.

Again, the rebound after opium increases with dose and length of administration, and this must be due to accumulation of uric acid and is relieved by its removal (see paper on "The Organic Factor in High Blood Pressure," *Medical Record*, New York, February, 1908).

And the rest of this observation shows that these patients were, during the continuance of the colic, unable to burn up and metabolise the whole of this sugar, so that some of it was eliminated in the urine; but as soon as the colic and collæmia departed, their metabolism was again equal to the task and the glycosuria ceased.

The fall of urea shows not only that the liver is implicated in lead colic, but that all the tissues of the body are implicated and have their metabolism hindered and their combustion reduced by the all-pervading collæmia, and similar transient glycosuria, no doubt similarly caused, is seen in cases of strangulated hernia, &c. (F. Neugebauer in *Wien. klin. Wochenschrift*, September 10, 1896).

The altered urinary pigments and the subicteric tint of the conjunctiva are also very interesting, but point rather to increased blood changes and destruction of cells, which are sure to take place as another result of the collæmia (see chapter xii.), than to any special

implication of the liver; though no doubt this important gland is implicated along with all the great metabolic tissues.

And this argument receives, I think, interesting confirmation from the researches of Dutournier and others, on what has been called "Bronzed Diabetes." See *British Medical Journal* Epitome, December 28, 1895, p. 101, where it is said that the above-named author "suggests that in these cases there is a decomposition of hæmoglobin, brought about by some as yet unknown cause." From my point of view the cause is well known, and the association of this slight hæmoglobinæmia with diabetes is completely explained by both being, as shown in this and the previous chapters, results of the same cause, collæmia.

Another case of bronzed diabetes is published in the *British Medical Journal*, 1903, vol. ii., p. 1052, by Dr. G. Parker, and in the discussion of the case many interesting points are mentioned. Thus he refers to the researches of Dr. Maude A. Abbott, who is quoted as saying that some unknown toxin leads not only to a blood destruction, but also to the destruction of the cells whose duty it is to remove the pigment.

Further on he suggests, after referring to the researches of A. C. Croftan, that a toxin causes cirrhosis of the pancreas, and thus furnishes excess of pigment and sugar, and that the same toxin affecting the liver prevents it from dealing with the pigment; hence may arise glycosuria, or pigmentation, or both.

He also refers to the close relation of many of these things to splenic anæmia and Banti's disease, and in a case probably of this nature that recently died under my care in the Metropolitan Hospital there was enlarged spleen without leucocythæmia, and very advanced cirrhosis of the liver, but no glycosuria. During life there was a marked lemon tint of the surface, but abundant sulpho-cyanide in the saliva showed that bile was passing freely into the duodenum. In all such cases there is no difficulty in accounting for congestion of spleen, pancreas and liver, for collæmia very obviously produces congestion of the liver, and this almost of necessity involves the other organs also. I have also several times come across cases of discoloration from the lemon tint above mentioned to a dark colour, reminding one of Addison's disease, in cases of more or less marked collæmia which I was treating for other troubles, and have seen these colorations completely disappear as the result of the changes produced by the uric-acid-free diet.

We know that uric acid by its effects on the circulation causes

congestion of the liver and all the viscera on the portal circulation, we know that it causes anæmia and destruction of red cells, and the case is fairly complete for the suggestion that the unknown toxin in these interesting conditions is merely uric acid.

A paper, which is of much interest in this connection, was published by Dr. L. P. Phillips in the Records of the Egyptian Government School of Medicine, of which he is professor, Cairo, 1904: "On the *Rôle* played by Malaria in the Production of Ascites." In this he shows that malaria probably accounts for as much as from 30 to 50 per cent. of the cases of ascites he records.

After what has been said above it is not very difficult to understand how malaria produces severe collæmia, and through this and its effects a chronic or recurring congestion of the liver and spleen; and there is this further point of interest, that we now know that treatment of the uric acid factor does much to modify and diminish the severity of many malarial symptoms, and may even cut short the attacks; while a uric-acid-free diet may render all symptoms much milder or entirely prevent attacks.

Some cases which it is interesting to bear in mind along with these are recorded by Professor Osler in the *British Medical Journal*, 1899, vol. ii., p. 1595, in a paper on "Hypertrophic Cirrhosis of the Liver with Bronzing of the Skin, Hæmochromatosis."

In one of these there were numerous attacks of purpura and urticaria on the skin of the legs; in the other there was a history of malaria in the Tropics, and in both there was enlargement of the liver and spleen in conjunction with progressive pigmentation and bronzing of the skin.

It seems to me that these cases must be very closely related to those of paroxysmal hæmoglobinuria and blackwater fever, discussed in a previous chapter, and after what has been said in this chapter on the relation of congestion of the liver to collæmia and to blood changes, and as to the causation of enlargement of liver, spleen and glands by uric acid in other chapters, there need be no difficulty in explaining the observed association of such important blood changes with enlargement of the liver and spleen and with chronic eruptions and pigmentation of the skin.

It follows from this that collæmia is the central factor in the causation of diabetes and that clearing the blood of uric acid will do good, while increasing the amount it holds in solution will do harm; and I have just pointed out that acids, opium, iodide of mercury, and other drugs which clear the blood of uric acid are useful; also that fevers and surgical operations, which have the

same effect on uric acid, diminish the output of sugar; while alkalies, which increase the uric acid, do harm.

Acids and opium often have a similar good effect in albuminuria; and a fever may not only, as I have shown, diminish the dropsy, but also reduce the output of albumin.

Then in reference to the interesting case of colic above mentioned in which glycosuria was produced, we have seen in fig. 61 that sugar follows the uric acid, rising when it rises, and falling when it falls; and it follows from this that, other things equal, there will be a larger excretion of sugar in the morning hours when the excretion of uric acid is large, and a smaller excretion in the evening hours in which the collæmia is slight, the blood granules scanty and the excretion of uric acid relatively small; and I see in an interesting paper by Dr. F. Kraus, jun., of Carlsbad, of which he kindly sent me a reprint, that this has actually been observed and recorded.

His paper has the title, "Notes on the Variation of Glycosuria in Diabetics," and appeared in the *Albany Medical Annals* of August, 1899.

He points out that several observers have noted that cases of diabetes which have reached a certain amount of tolerance for carbohydrates show a measurable amount of glucose in the urine if they take the smallest amount of carbohydrates for breakfast, although they are able to assimilate large quantities perfectly if taken later in the day.

He then records two cases, in the first of which 50 grm. of bread at breakfast caused glycosuria, while four times that quantity later in the day did not do so.

In the second case 30 grm. of bread at breakfast produced glycosuria, but he could take 120 grm. in the day without glycosuria if given at the later meals.

He also mentions a case recorded by Naunyn, a diabetic patient, aged 28, who became glycosuric when only 5 grm. of bread were taken at breakfast, but could take 100 grm. bread, 60 to 70 grm. potatoes and an apple later in the day without glycosuria.

The explanation given by Naunyn, which Dr. Kraus quotes, is "that in the empty intestines the introduced carbohydrates more quickly digest and absorb, and so the diabetic organism is supplied with more sugar at once than it can assimilate."

It seems to me that those who have regarded diabetes from any and every point of view except as a failure of combustion, which it really is, have here put forward an explanation of the facts

observed which will not cover them; for we have seen, in the last chapter, especially with regard to my reference to fig. 3, that the rise of urea which follows breakfast is slower and less marked than that after the later meals of the day. Are we to conclude that the carbohydrates are more quickly digested and metabolised in the morning, while the albumens, on the contrary, are more slowly dealt with?

We know why the rise of urea is slow and less marked after breakfast; it is but a single instance of the universal law that urea falls with high and rising uric acid, and rises with low and falling uric acid; that in the collæmia of high uric acid, circulation, digestion, metabolism, and combustion are all slowed down, and neither albumens, carbohydrates nor fats are quickly digested or metabolised.

We have seen in fig. 61 that sugar follows uric acid, being high when it is high and low when it is low, and in this respect it exactly follows another urinary product of defective combustion—albumin. This also is high when uric acid is high and low when it is low; and we have seen in the previous chapter that by controlling the uric acid we can control the albumin, and that as we bring down the albumin up goes the product of its final metabolism, the urea.

Albumin and sugar, then, are the indices of incomplete combustion, and that is the reason they move together and in the opposite direction to urea, which is the index of complete combustion.

But as we have seen in the previous chapter, albumin in Bright's disease is like sugar in diabetes, always more after breakfast in the morning than after other meals later in the day; but if this rise of albumin after breakfast is due to increased absorption of albumens from an empty digestive canal, why is it that urea is lowest at that time and rises less than after other meals? For, as a rule, and as I have shown in my figures in "Diet and Food," urea is the index of digestibility and of the rapidity of digestion and absorption, so that we are landed in a contradiction.

There is only one explanation that will relieve us of this contradiction and meet all the facts of the case; albumin we know is a product of defective combustion, hence it rises and falls with the uric acid in the blood and urine, and urea moves in the opposite direction.

Sugar bears exactly the same relation to uric acid because it is also a product of defective combustion. Are we to believe that in the absorption of a food like bread the carbohydrates are taken up four

times as quickly after breakfast as after any other meal, while the albumens which surround them are not only not taken up more quickly but actually more slowly? or are we to believe the only complete explanation of all the facts, that sugar is high in the morning just as albumin is high and urea low, because uric acid is high, and because uric acid collæmia causes, as we can also see for ourselves, defective capillary circulation, nutrition and combustion throughout the whole body in the morning hours?

Dr. Kraus goes on (previous reference): "A similar fact, in the contrary sense, is the paradoxical diminution of glycosuria connected with gastro-intestinal troubles (von Noorden), where, with equal amounts of carbohydrates in the food, less glucose appears in the urine, the result of diminished digestion and diminished and retarded resorption."

I have quoted the passage in full, but it certainly seems to me to be by no means a similar fact, but one of the very opposite meaning, for if, as I have always insisted it should be, urea is estimated along with sugar we shall at once see an important difference between the rise of sugar after breakfast and the fall of sugar which takes place in conditions of diminished absorption of foods from gastro-intestinal disturbance and dyspepsia.

For, as I have over and over again pointed out, in diabetes if we irritate the stomach or intestines, or allow any food to upset them, or give opium, which diminishes appetite and the taking of food, sugar and urea fall *together*, that is, they move in the same direction.

But we have seen that in the case of breakfast, sugar and urea move in *opposite* directions: the sugar rises more quickly than usual, while the urea rises more slowly than usual.

It is clear, then, that the rise of sugar in the urine after breakfast is not due to increased absorption of sugar into the system but to diminished combustion in the system; later in the day, with four to twenty times the amount of bread taken, the absorption of carbohydrates is no doubt far larger in the given time; but now the collæmia has diminished, the capillary reflux has quickened, circulation, nutrition and combustion have improved, the fires of life burn up brightly, and there is no sugar left uncombusted, no glycæmia and no glycosuria.

The completeness of the parallelism between albuminuria and glycosuria here brought out will not escape notice, and we are at once provided with an index of the cause of their fluctuations, for changes in their excretion which are due to defective combustion

move in the opposite direction to urea, while those which are merely due to differences of absorption of food move in the same direction with it. Water, a result of free capillary circulation, and urea, a product of complete combustion, move in the opposite direction to uric acid. Albumen and sugar, products of deficient circulation and defective combustion, move in the same direction with it.

Dr. Kraus goes on to point out that the facts above mentioned show the importance of not merely regulating diet as to quantity and quality, but also in reference to time of day.

He remarks that it is only in mild cases of diabetes that such regular fluctuations are met with; but if my explanation of the facts is correct the indication for treatment applies to all cases, for in all combustion is at its worst in the morning hours; but in bad cases there is more uric acid, and collæmia is severe nearly all day, so that changes are less evident though probably still there.

I am interested to see also that Krehl (*Centralbl. für innere Med.*, 1897, No. 40) found in some experiments he made on students at Jéna that five had glycosuria out of fourteen who drank beer in the morning, but out of nineteen who drank it in the evening only one had glycosuria.

Here is an almost exact reproduction of the experiment I proposed to make in a previous chapter with a test meal of albumens in cases of defective combustion bordering on Bright's disease. The worse the combustion the slower the rise of urea.

No doubt the capillary reflux would have been found slower and the blood pressure higher in the five students who had glycosuria than in the nine who had none.

The record also shows that combustion can be directly tested both with sugar and albumen, and thus the direction in which it is most likely to fail can be predicted, so that prevention may be improved and made more precise. And in patients with slow capillary reflux we may be able in this way to tell several years beforehand whether their defective combustion will eventually affect the albumens or the sugars or both, while the defective combustion of fats so common in middle life (when the retention period of good nutrition is coming to an end and the collæmia of declining life is establishing itself—see chapter v.) speaks for itself in the form of obesity. It may be said that uric acid is itself a product of defective combustion, and therefore moves with other similar products (albumin and sugar) but everything (diet or drug) that clears the blood of uric acid improves combustion and raises urea even in physiology.

The action of mercury, as some think, on the liver is not peculiar

to mercury nor specially on the liver, for it is a result of clearing the general circulation of uric acid, and the same effect is produced by a dose of uric acid itself or by caffein or theobromin, or more slowly by the uric-acid-free diet, and the only factor common to all these is diminished uric acid in the circulation. Mercury, uric acid and the xanthins clear it directly by uric acid filter action, diet indirectly and slowly by diminishing introduction. Mercury has no special action on the liver, it frees the capillaries all over the body; caffein does the same or uric acid itself, and this whether injected into the circulation or swallowed.

Some say that carbohydrates congest the liver and cause an increase of uric acid and all other products of defective combustion. It is easy to show that this is not so, for there is more carbohydrate in the uric-acid-free diet than in ordinary diet, and yet the former always diminishes the output of uric acid in relation to urea, and often suffices to cure mild cases both of albuminuria and glycosuria without the use of any drugs (see cases in this and previous chapter, also fig. 73).

I shall now show that salicylates, which clear the blood of uric acid by effecting its elimination, are also very useful in glycosuria and diabetes, just as we have seen in chapter viii. that they are useful in preventing collæmia and fatigue; for a favourable record of results of their use in glycosuria and diabetes, see paper by Dr. R. T. Williamson, *British Medical Journal*, 1901, vol. i., p. 760.

Mary A. D., aged 55.—An out-patient at the Royal Hospital in January, 1888. Complains of thirst and irritation of vulva. Urine pale amber, 1020; 3·2 per cent. sugar. Alkalies and nux vomica no effect. After four weeks of salicylate, urine 1014, with no sugar. Drinks much less. Salicylate left off, and in two weeks urine 1020 and 3 per cent. of sugar, and again salicylate reduced it to 1011 and no sugar.

Mrs. C., aged 45.—May, 1888. Urine 1032—1040, containing 5 per cent. sugar. Put on salicylate, and in seven days' time the urine was 1035 and 2·5 per cent. sugar. Treatment continued, and two weeks later urine dark amber, 1030, and only ·5 per cent. of sugar. Drinks much less.

I then altered her diet; left off the excess of meat she was taking, and put her on milk, fruit, and vegetables, and so long as she took the salicylate these did not increase the sugar, except on one occasion when it reached 1·6 per cent. She found that potatoes were worse than other vegetables, and produced diuresis (probably

from the large amount of alkali they contain interfering with the action of the salicylate, see fig. 8). She attended for many months, the sugar in spite of the above diet keeping about 1· per cent.

Her husband then left the district in search of work, but a year later (October, 1889) she came back asking for more of the medicine which had done her so much good. She is paler, and has wasted considerably since last seen in 1888. Urine is now 1030 : contains 5·7 per cent. of sugar, urea 1·5 per cent., and uric acid ·08736 per cent., uric acid to urea 1—17, urea to sugar 1—3·8, a large excretion of uric acid, and no doubt collæmia contemporaneous with glycosuria. Fourteen days later, after a course of salicylate, the urine only contained ·6 per cent. of sugar.

November, 1890.—Returned again after considerable absence, and again salicylates reduced her sugar in a week to 2·5 per cent. She was, however, upset by home troubles, and could not take her medicine or attend regularly.

February 16, 1891.—Took her into the Royal Waterloo Hospital. No drugs except a little dilute phosphoric acid, a little sal volatile for feelings of "weakness and sinking" (patient probably indulges in alcohol at home for these feelings). Urine of twenty-four hours 990 cc., 1046. Sugar 7·1 per cent., urea 1·6 per cent., uric acid ·06720 per cent. Uric acid to urea 1—23. Urea to sugar 1—4·4. Total sugar 2·4 oz.

Here we see very clearly what I believe occurs in all cases, a progressive increase of sugar, together with increasing debility as time goes on.

The first slackening of combustion causes eventually debility, and debility of that most important muscle, the heart, causes a constant increase in the defect of combustion, even if the collæmia factor does not also increase.

Here we have, just as we have already seen in Bright's disease, a vicious circle—defective combustion, heart weakness, increased defective combustion, increased heart weakness, and so on, steadily downward.

Here also, just as in Bright's disease, the onset of the disease means collæmia, intensified by heart weakness or failure; hence the origin of diabetes, just as of Bright's disease, in pregnancy, associated no doubt with some absolute or relative heart failure (see case of Jane B., to be mentioned later); hence in diabetes just as in Bright's disease we have not only to clear up the primary collæmia, but have also to save and strengthen the heart muscle by every means in our power.

On February 26, after ten days on salicylates, urine was 1335 cc., 1034, urea 1·5 per cent., sugar 3·6 per cent. Urea to sugar 1—2·4. Total sugar 1·6 oz. Salicylates had here reduced the total sugar, and had also reduced it relatively to the urea, which is the safest guide of all.

She remained in for several weeks, during which the sugar was reduced to 2 per cent. or less, with the relation of urea to sugar 1—1·2. Patient, however, became unruly, dissatisfied and disobedient, possibly owing to alcohol and stimulants being cut off, and took her discharge.

During the first part of her time in hospital she was menstruating, and this appeared to increase the feelings of sinking and faintness, as it doubtless also lowered the acidity, produced increase of collæmia, and also interfered with the full action of the salicylates.

Jane B., aged 33, November, 1888.—Complaints of weakness and languor; drinks all day long and passes much water, especially during last two months. She first noticed excessive thirst about eighteen months ago, the time of commencement of her last pregnancy (see previous remarks). Urine pale amber, 1043, urea ·6 per cent., uric acid ·02016 per cent., sugar 10 per cent. Uric acid to urea 1—30, urea to sugar 1—17. She was given some instructions about diet and put on alkalies and nux vomica. These did no good, and at the end of a week sugar was still 10 per cent.

December 1.—She was put on salicylate, and told to try and estimate the quantity of water in twenty-four hours.

December 8.—Urine 1040; sugar 9 per cent.

December 16.—Passed twenty pints of urine yesterday; thinks she has passed considerably more than this. Urine 1042. Sugar 8 per cent. Urea to sugar 1—12.

After this sugar fell steadily to 7 per cent., with relation to urea 1—8·7, and she began to gain weight and get more colour.

In April, 1889, during my absence, salicylate was stopped and nux vomica and alkalies repeated; the mixture made her worse, and she threw it away after two or three doses. (It is a remarkable fact that patients with glycosuria or diabetes say that alkalies make them worse and acids make them feel better. The former increase but the latter diminish collæmia.)

She did not come again till August 17, when she was obviously worse—pale, feeble and with quick pulse. No urine brought; given salicylate again.

August 24, 1889.—Better and less thirst; when thirst is great

nothing under two pints of water is any use. Urine to-day 1040, sugar 10 per cent.

In September urine had fallen to ten pints a day, sugar 6 per cent., and urea to sugar 1—6; and at the end of this month sugar was 5·5 per cent. and urea 1—5·5.

In October, sugar 5 per cent. and urea to sugar 1—5, and she got on so well that she refused to leave her children and come into hospital.

The urine was reduced to less than one-half of the original amount, and the percentage of sugar to one-half also, so that the total sugar was reduced to one-fourth of the original quantity, and the relation of urea to sugar altered from 1—17 to 1—5.

She improved and felt better in every way while taking the salicylate, and while the sugar was diminishing she steadily increased in weight.

She continued to attend for many months after this, and so long as she took the salicylate did well. I found that small doses of morphine increased its effect, and gave her for some time gr. $\frac{1}{6}$ in pill three times a day. By this means sugar was reduced to 4·5 per cent., and on one occasion to 3·5 per cent. But unfortunately, in the spring of 1890 there was a change; she again became pregnant, and this produced a considerable amount of vomiting; this interfered with the taking and action of the salicylate, and she went rapidly down hill. She still obstinately refused to come in, and soon ceased to attend. My last note is dated October 7, 1890, when she was much weaker and worse, and salicylate had been left off for some time and bismuth and other treatment of symptoms made use of. As she refused to come in, in spite of all I could say, nothing more could be done, and I fear that she soon died.

The case, however, illustrates well the power of salicylates in severe diabetes; and I have no doubt that the drug prolonged her life by at least two years, as when I first saw her I did not expect her to live a month, and but for her unfortunately again becoming pregnant (which is in itself strong testimony to the improvement in her condition) still better results might have been obtained.

With regard to the patient's history and the fact that her diabetes probably originated in a pregnancy, we have seen that in her last pregnancy she had considerable vomiting and then got much worse, and I think that in her former pregnancy there was vomiting also, and the diabetes originated in the severe collæmia and heart failure thus produced. In this case almost every word written in the last chapter with regard to the causation of albuminuria in

pregnancy would apply equally well to the causation of this diabetes; only in the one case the defective combustion affected the starches and sugars, in the other the albumens, and in some intermediate cases as we know it may affect both, or now one and now the other alternately. I think that if this patient had had normal pregnancies free from vomiting, which increased both collæmia and heart failure, she might have been alive still and possibly never have had diabetes. So that if Bright's disease is collæmia, plus cold, plus heart failure, diabetes is also collæmia plus heart failure, both these conditions tending, as we have seen, to produce congestion of the liver, the chief pathological change met with in diabetes.

Another case is that of Winifred H. F., aged 8 years, who was admitted into the Royal Waterloo Hospital, January 22, 1891.

Complained of thirst and nocturnal urination; pale, wasted; weight 2 st. 5 lb. Some increase of liver dulness, and constipation.

Urine 2,220 cc., pale amber, 1040. Sugar 5·5 per cent., uric acid to urea 1—33. (No excess of uric acid [?] due to phosphoric acid given as a drink.) Urea to sugar 1—5·5, urea per lb. 10·3 gr. She was put on diabetic diet; no drugs except a little dil. phosphoric acid.

The sugar fell to 5 per cent. and then to 4·1 per cent., but urea fell very considerably also, and on February 9 it was only 4·6 gr. to lb. Diet here was interfering seriously with nutrition, and though sugar fell, urea fell more; very different from what had occurred in the previous case with salicylate (see also previous remarks on relative movements of urea and sugar).

She was given some salicylate, but it unfortunately upset the stomach and made the failure of nutrition greater; sugar and urea both falling considerably. Her pulse on several occasions was relatively slow, showed considerable high tension and occasional intermissions.

The salicylate was therefore stopped, and she was given two pints of milk and some brandy. She had previously been taking food (diabetic diet) badly; but she liked the milk and began to improve on it, and urea and sugar both increased.

February 12.—When urea got back to 9 gr. or 10 gr. per lb. and sugar to 5 per cent. salicylate was again given in small, slowly increasing doses. Both urea and sugar, however, continued to increase, though on February 18 urea was to sugar 1—3·2, and on the 19th 1—3, and on the 21st 1 to 2·9, and on the 24th 1 to 2·3.

Salicylates now apparently caused some dyspepsia and diarrhœa,

and all drugs were therefore stopped, and on February 28 urea was to sugar 1—3·3. It looked, therefore, as if the salicylate had had some effect in lessening the sugar relatively to the urea.

March 2.—Slight rise of temperature, and sugar fell in consequence, the urea relation being 1—2·2.

Salicylate was begun again, gr. vii. four times a day, but again diarrhœa followed its use and some tr. opii was given.

March 4.—Urea to sugar 1—3·1; salicylate had not begun to act.

March 5.—1—3.

March 7.—1—2·3.

March 12.—Opium stopped. Given codeina gr. ¼ three times a day, and salicylate gr. x. four times a day; urea to sugar 1—2·2.

March 18.—Rather more languid. Codeina stopped and liq. morph. hydroch. ɱx. given four times a day with the salicylate.

March 26.—Going on much the same, but there is occasionally some vomiting, and the diarrhœa has not completely ceased. Urea to sugar 1—2·2. Total urea 739 gr., or 22 gr. per lb. She is now taking a considerable quantity of milk and is not kept on strict diabetic diet, as it was found that she took this badly; urea diminished, and she got into a lethargic condition, which disappeared as the diet improved.

March 27.—Some diarrhœa again, so salicylate and morphine stopped.

March 31.—No diarrhœa or vomiting; given codeina gr. ¼ three times a day.

April 4.—On codeina; temperature raised to 101° F. Takes badly and has some nausea; urea to sugar 1—2·5 (effect of fever), but urea has fallen to 540 gr., 16 gr. per pound.

April 6.—Not so well; very drowsy, especially in the morning after breakfast, when she falls asleep and does not wake for several hours. Takes badly, some nausea. All drugs stopped, milk increased to 3 pints, brandy 2 oz.

April 9.—Better and brighter much; takes better, but urine has increased in quantity and specific gravity. Salicylate and morphine mixture repeated.

She died on April 19 (while I was away for a holiday) with some symptoms of diphtheria, and another child in the ward had a suspicious throat and was isolated.

Permission for a *post-mortem* examination could not be obtained, so the exact nature of the case remains in doubt. There was no optic neuritis, and such vomiting as occurred seemed to be the result of drugs rather than of any central cause. The only physical sign was a moderately well marked increase of liver dulness.

As to drugs, the salicylates on several occasions reduced the sugar relatively to the urea, and that without in any way reducing the urea.

The codeina diminished both urea and sugar (*i.e.*, it diminished appetite, digestion and absorption); but the salicylate diminished the sugar relatively to the urea (*i.e.*, it increased the combustion). On one occasion the codeina appeared to cause drowsiness.

Diabetic diet was an absolute failure, causing a great fall of urea and producing a lethargic condition which would no doubt have been fatal if the diet had not been improved; possibly diet was begun too suddenly. This is in complete accord with the observation of Hirschfeld (*Deutsch. med. Woch.*, June 27, 1895) that inanition is the cause of the coma in diabetes; and my own observation decidedly leads me to agree with him, for I have in several other cases noted the approach of such conditions along with a marked fall in urea, and if I could run up the urea, as above, by increasing the milk, I appeared to be able to ward off the coma. It has also been pointed out by Maurel (*Bull. gen. de Thérapeutique*, 1897) that milk diet wards off both the gangrene and coma of diabetes. In such cases it is obviously of the greatest importance to examine the urea; anything that interferes with the taking and digestion of food will reduce both sugar and urea, but this is not a curative action. Salicylate reduced the sugar relatively to the urea, and the child fully held her own while taking it. Unfortunately, however, it appeared to produce some nausea and diarrhœa.

In an interesting paper in the *British Medical Journal*, 1903, vol. ii., p. 1630, Dr. J. E. H. Sawyer points out that: "In diabetic coma the bodily temperature is nearly always subnormal." He also shows that the subnormal temperature is not the result of the excretion of sugar, as it does not vary with the quantity of sugar. He finds also a subnormal temperature in uræmia. It is not difficult to see that excess of uric acid in the blood and falling urea may easily account for subnormal temperature in diabetic coma, and I should expect that the temperature would be found to vary with these things and not with the sugar, for though I have shown that uric acid and sugar rise and fall together, this is only true so long as digestion is fair and the supply of sugar good; once let appetite and digestion fail, as they do in coma, then the sugar will fall along with the urea, and for the same reason, and sugar and uric acid will move in opposite directions.

Therefore, though the coma is proportional to the collæmia and

its results, the high blood pressure and the fall of urea, it is not here proportional to the sugar.

I shall also give the notes of a case in which salicylates given along with small doses of calomel eventually acted well, though at first they appeared to fail.

W. H., aged 36. Admitted under my care in the Metropolitan Hospital, January 18, 1893. Complains of increase of appetite one month and increase of thirst two weeks.

His father is alive and well, but suffers from lumbago and piles occasionally.

His mother has "rheumatics" in the hands. He has five sisters, who are well.

Patient has not had any fevers, not even the influenza.

His tongue is slightly red at the tip and edges, but not specially clean.

His bowels are constipated.

There are no physical signs.

January 19.—Weight, 92 lb. 10 oz. Put on a modified diet, gluten bread. Milk 2 pints and imperial drink without sugar. No potatoes, bread or sugar.

January 22.—Urine, 74 oz.; specific gravity 1035. Acid. No albumin. Sugar, 3·1 per cent. = 1,059 gr.; urea, 2·4 per cent. = 819 gr.; relation, 1—1·2.

January 24.—Bowels opened by mist. sennæ co. Thirst is rather less.

January 28.—Sodii salicyl. gr. xv., with aq. menth. pip., given every six hours. Weight, 103 lb.

February 1.—Urine, 58 oz.; specific gravity 1036; sugar, 3·1 per cent. = 830 gr.; urea, 2·6 = 696 gr.; relation, 1—1·11.

The salicylate appears to cause some nausea, and he is not taking his food so well. Try to take the salicylate in powder.

February 4.—Urine, 56 oz.; sugar, 1·4 per cent. = 361 gr.; urea, 2·4 per cent. = 620 gr.; relation, 1—0·58. Weight, 103 lb. 8 oz.

Appetite still bad, so salicylate was stopped and iodide of sodium gr. vii. given in place of it three times a day.

Here we see again that the sugar has fallen greatly down to almost one-third of the amount on January 22, but urea has also fallen by as much as 200 gr., and we know that this was due to deficient income of food from nausea and loss of appetite, and if we add, say, 200 gr. to the sugar on this account, the relation would come out nearly 1—1, or close to what it was on February 1.

February 8.—Urine, 98 oz.; urea, 2·1 per cent. = 950 gr.; sugar, 2·0 = 905 gr.; relation, 1—0·95. Iodide increased to gr. x.

February 10.—Urine, 80 oz.; urea, 2·4 per cent. = 837 gr.; sugar, 3·1 per cent. = 1,145 gr.; relation, 1—1·2. Weight, 103 lb. 8 oz.

February 14.—Iodide left off, and salicylate again given in different form.

February 15.—Urine, 90 oz.; urea, 2·4 per cent. = 997 gr.; sugar, 3·3 per cent. = 1,372 gr.; relation, 1—1·3.

February 18.—Urine, 94 oz., specific gravity, 1037; urea, 2·7 per cent. = 1,130 gr.; sugar, 2·6 per cent. = 1,088 gr.; relation, 1—·96. Weight, 105 lb. 6 oz.

February 22.—Urine, 86 oz., specific gravity, 1031; urea, 2·3 per cent. = 913 gr.; sugar, 2·5 per cent. = 993 gr.; relation, 1—1 (nearly).

February 25.—Urine, 102 oz., specific gravity, 1036; urea, 2·3 per cent. = 1,082 gr.; sugar, 2·9 per cent. = 1,365 gr.; relation, 1—1·2. Weight, 106 lb.

Here, again, though the salicylate at first reduced the sugar relatively to urea, the improvement was not maintained.

Liq. morph. hydrochlor. ♏xii. was added to each dose of the mixture.

March 1.—Urine, 46 oz.; urea, 2·7 per cent. = 572 gr.; sugar, 1·2 per cent. = 254 gr.; relation, 1—·44. Weight, 106 lb. 4 oz.

Here, again, a great diminution of sugar, but also a great fall of urea, and no doubt the salicylate and the morphine upset appetite and digestion and accounted for this.

March 8.—Urine, 71 oz., specific gravity, 1032; urea, 2·0 per cent. = 710 gr.; sugar, 2·0 per cent. = 710 gr.; relation, 1—1.

March 10.—Urine, 73 oz., specific gravity, 1024; urea, 2·2 per cent. = 791 gr.; sugar, ·8 per cent. = 287 gr.; relation, 1—·36. Weight, 106 lb. 8 oz.

Here is some improvement, and, as urea is rising, it is probably due to the drugs.

March 14.—Urine, 64 oz., specific gravity, 1025; urea, 2·7 per cent. = 797 gr.; sugar, ·5 per cent. = 147 gr.; relation, 1—·19. Allowed a small bit of toasted bread twice a day.

March 17.—Urine, 70 oz., specific gravity, 1023; urea, 2·4 per cent. = 776 gr.; sugar, ·75 per cent. = 241 gr.; relation, 1—·3. Weight, 107 lb. 4 oz.

March 24.—Weight, 108 lb. 8 oz.

March 29.—Urine, 74 oz., specific gravity, 1036; urea, 2·4 per cent. = 751 gr.; sugar, 3·3 per cent. = 1,127 gr.; relation, 1—1·5.

Toast was left off and liquor. pancreaticus given, also calomel gr. ½ twice daily.

April 1.—Urine 62 oz.; urea, 2·7 per cent. = 773 gr.; sugar, 2·5 per cent. = 716 gr.; relation, 1—·9; weight, 106 lb.

April 11.—Has had vomiting in the morning since 6th. Urine, 44 oz.; urea, 3·5 per cent. = 711 gr.; sugar, ·5 per cent. = 101 gr.; relation, 1—·14.

April 14.—Weight, 108 lb.

April 19.—Urine, 54 oz., specific gravity, 1026; urea, 3·3 per cent. = 822 gr.; sugar, ·7 per cent. = 174 gr.; relation, 1—·21.

April 22.—Has had some pain in connection with the sac of a femoral hernia, but this has now been relieved by rest and ice locally. Urine, 52 oz., specific gravity, 1021; urea, 2·1 per cent. = 508 gr.; sugar, ·15 per cent. = 20 gr.; relation, 1—·03.

April 26.—Urine, 44 oz., high colour, specific gravity, 1030; urea, 3·8 per cent. = 671 gr.; sugar, ·4 per cent. = 81 gr.; relation, 1—·1. Weight, 104 lb. 12 oz.; given claret, ℥ ii.

April 29.—Urine, 64 oz., specific gravity, 1019; urea, 2 per cent. = 591 gr.; sugar, ·1 per cent. = 56 gr.; relation, 1—·09.

May 3.—Urine, 38 oz., specific gravity, 1030; urea, 3·4 per cent. = 595 gr.; sugar, ·03 per cent. = ? *nil.*

Here sugar is reduced to *nil*, though urea is as high as at last note. Toast allowed again.

Is still on salicylate, morphine, calomel and liq. pancreaticus.

May 6.—Urine, 48 oz., specific gravity, 1029; urea, 3·2 per cent. = 708 gr.; sugar, none; weight, 104 lb.; liq. pancreaticus left off.

May 10.—Quantity and specific gravity as at last note; still no sugar.

May 13.—Weight 106 lb.

May 19.—As sugar continued to be absent and he was going on well, he was allowed to go out, taking the salicylate mixture and calomel with him.

August.—Attends at the hospital every few weeks and continues the mixture and the calomel powders. Sugar remains absent and he is quite holding his own.

I think the credit of this improvement remains with the salicylate and calomel; the liq. pancreaticus appeared to have no effect whatever; the salicylate and morphine also appeared to account for an improvement in March.

As mentioned in a previous case, morphine helps the action of a salicylate, and I believe that it may do this by keeping up the

acidity and preventing any of the uric acid which salicylates bring through the blood from getting into combination with an alkali, because it is the combination of uric acid with an alkali which affects the circulation and does all the harm to the combustion.

And my object in giving calomel was just the same, namely, to keep the blood clear of uric acid combined with an alkali; and calomel does this by directly combining with the uric acid (see fig. 17), and it appears from the results in this case that it helps the action of the salicylate more than the morphine does, possibly because its effects are independent of acidity; and under certain conditions the morphine may not be able to raise the acidity (see fig. 15).

Considering that in this case there was only 3·1 per cent. of sugar to begin with (though, by the way, this was on diet), I should have expected a more decisive result with salicylates alone; but their partial failure was, I think, largely due to their being taken badly and producing nausea; when they do this they are no use in any case. They are also no use when there is nausea or vomiting from other causes (see case of Jane B.). I believe, because there is then so much alkali in the blood, that a good deal of the uric acid is sure to combine with it.

Still, I consider that given along with acids or small doses of morphine or calomel, the salicylates are the most useful drugs we possess for the treatment of these troubles, and they act by eliminating uric acid, and so clearing the blood of it. I have often seen the sugar greatly reduced by opium or codeina, but they have also appeared to me to reduce urea very considerably at the same time, while with the best action of the salicylates urea rises.

Frerichs says that salicylates reduce sugar by interfering with digestion, but in several of my cases salicylates not only greatly reduced the sugar without reducing urea, but the patients steadily gained weight while taking them.

In my paper on the use of salicylates in diabetes I mentioned that two cases had been reported as cured by them, and since my paper I have heard from others who have followed up my suggestions and used them with great benefit (see Dr. Mansel Sympson, *Practitioner*, August, 1891); and Dr. Brooks, of Lincoln, read a paper before the Lincoln Medical Society in 1891, "On the Use of Salicylates in Diabetes."

To illustrate the possible relationship between diabetes and the uric acid headache, I will now give a few notes of the case of Edith R., aged 29, single, admitted into the Royal Waterloo Hos-

pital in October, 1897. She complained of loss of weight for nine months. Abdominal pain and absence of menstruation for three months. She is the youngest of three, having two brothers older. Her father died of phthisis at the age of 47. Her mother is alive, but has always suffered from bilious headache. The patient herself has been subject to bilious attacks with headache every three weeks since childhood. Her tongue is red and clean. Pulse fast, 92. The second sound of the heart is loud at the right base, but at that time I had no means of accurately estimating capillary circulation and blood pressure. The abdomen was slightly distended and tender all over; there was some little pain in the left inguinal region. The liver dulness was full large, but its edge was not felt. Urine on admission, 1040, passes from 80 to 100 oz. per day, containing 7 to 8 per cent. of sugar.

Unfortunately she was only in hospital for a short time, during which she was gradually got on to diabetic diet, and just as we were going to watch her carefully with a view to testing the action of drugs she went out, as her family had left London for the North of England and she wished to follow.

I give the case merely for the history, and I may say that I have had another similar case in private, in which a lifelong migraine was followed, later in life than in the above case, by diabetes.

A more recent case of the same sequence is that of M. B., female, aged 57, sent to me by Dr. Monro-Grier, of Mevagissey. Pulse 84; capillary reflux 8; blood pressure 150. Subject to sick headaches all her life. Has had several attacks of vertigo and one attack of temporary coma. Has both gout and rheumatism in her family, and her mother died of gall-stone. Urine 1028, pale amber, minute trace of albumin, and sugar 6 per cent. Urine 60—80 oz. per diem. Highest specific gravity observed, 1035.

Israel W., aged 31, admitted into the Metropolitan Hospital in April, 1898. He made the usual complaints of thirst and loss of weight, and had no prominent physical signs in head, chest, or abdomen. His weight on admission was 7 st. 11 lb. 8 oz. Urine was from 80—100 oz. in twenty-four hours, specific gravity 1042, and contained from 35—40 gr. of sugar to the ounce.

His capillary circulation was slow, his blood pressure high, and his left radial artery measured with Oliver's arteriometer 1·3 to 1·4 mm. The first sound of the heart was long and the second sound loud at the base and apex, the ordinary signs of rather high blood pressure, and the above arterial measurement is large, relatively, as the patient is a small man.

He was put on diabetic diet, and possibly the change was made too suddenly, as he lost weight considerably, falling to 7 st. 0 lb. 8 oz. in the first few weeks. This diet reduced the urine somewhat, but he was still passing a considerable quantity, containing fully 30 gr. of sugar to the ounce. He was now put on the following treatment, the alteration on to which was made gradually, and he was given salicylate of soda gr. xv. three times a day.

Milk, 2 pints.
Cheese, 2 oz.
Mutton or fish, 2 oz.
Four* protene diabetic biscuits.
Gluten bread, 3 oz.

No tea or coffee, a little green vegetable with salad oil.

It was my intention to have cut off all animal flesh, thus stopping as far as possible all introduction of uric acid, but the patient was very fond of meat or fish, and lost weight if they were further reduced or cut off. On this diet the patient quickly regained the weight lost, and the water and sugar steadily diminished, so that in two or three months the urine was about 60 oz., containing about 10 gr. of sugar to the ounce, a total excretion of 600 gr. of sugar in place of 3,500 gr. per day. The same treatment was continued, though he occasionally had the salicylate four times a day instead of three times, and now and again for a few weeks ½ gr. of calomel two or three times a day in addition. In October, 1898, his weight was 7 st. 12 lb. and steady, his urine from 40—50 oz., specific gravity 1032, containing 6 gr. to ounce of sugar, and some days (six or eight in the month) only 4 gr. to ounce, a total daily excretion of sugar of only 160 gr.

His condition in May, 1899, was as follows: Weight 7 st. 11 lb. 12 oz., steady. Urine, 40—50 oz., containing from 6—10 gr. of sugar to the ounce in spite of two pieces of ordinary bread toasted (about 1½ oz. bread each) being added to the above diet. And this, I should say, has been done all along since the sugar fell the previous summer to comparatively insignificant quantities; when the sugar is at 4 or 5 gr. to the ounce I give him three pieces of toast, but if the sugar rises I diminish to two pieces. His capillary circulation is still slow, capillary reflux 6—8; probably it was still slower when he came in. His heart still gives the signs of high blood pressure, but also of some heart failure, as its rate is quick, 80—90 and above, and the blood pressure in 135.

* Protene is the albumin of milk freed from sugar and fat, and can be obtained from "Protene," Limited, 36, Welbeck Street, London, W.

He had some excess of blood granules, 1—9, and this was probably more marked when he first came in, but it was not recorded. The colour of tongue and gums is now fair, not much below normal, and this is probably an improvement on his original condition.

Israel W. remains under my care. He was sent out for a month or two in the autumn of 1899 to see how he would get on without treatment and on such diet as he could manage for himself; but he got decidedly worse and lost weight, falling down to 7 st. when he came back to us in December.

January, 1900: he has again improved; he is back on the diet above mentioned and is taking salicylate of soda gr. xv. three or four times a day; with this, sugar has diminished and weight has again gone up to 7 st. 9 lb. 10 oz., but his capillary reflux is still slow and his blood pressure still raised; his pulse is still quick and tends to quicken more and more as time goes on, and it is, I think, this progressive failure of the heart before the obstructed capillaries that drags him down and prevents his attaining complete combustion.

This patient remained under my care till April, 1902, when he went home to Russia at his own wish. He held his own, and the last record of weight was 7 st. 9 lb.

I think we should have done better in his case if we had been able to alter his diet completely, leaving out all meat and fish, as was done in the successful cases of Bright's disease; and the drugs do not succeed or do so only with much greater difficulty even in Bright's disease if this cannot be done. This we see in the case of Mary W., and I may say that I have since been treating her as an out-patient, and having persuaded her to alter her diet she is improving more quickly, and blood pressure is falling decidedly.

For contrast with the above, and as showing perhaps the original condition of his circulation, I give the notes of Fred E., aged 32, admitted under my care more recently, who is being slowly got on to diet and having no drugs. Urine 130 oz. and above, specific gravity 1040—1044. Sugar 38—40 gr. per ounce. Pulse slow, 56—58, and the heart gives the signs of high blood pressure as in the case of I. W. Blood pressure 180. Capillary reflux 7—8, half seconds. Blood granules to red cells 1—4. Colour in tongue and gums is bad, probably less than half the normal, say blood decimal ·4.

It seems that diabetes has increased decidedly in the last twenty-five years, a fact which I should have no hesitation in correlating with the simultaneous increase of many uric acid troubles and the

increased consumption of flesh and tea which have marked the same period.

Some consider alcohol an important factor in this increase, and no doubt alcohol will help in the production of congestion of the liver, but alcohol-taking is itself a result of collæmia.

Another point of interest is the relation of diabetes to injury or shock, or even to wear and tear and an anxious life. The mechanism is in all these cases the same.

We already know that shock has a relation to chorea and to Graves' disease, both being troubles associated with collæmia.

How does shock, injury, or anxiety give rise to collæmia and intensify its high blood pressure effects?

We already know (chapter viii.) that shock causes stoppage of digestion and a fall of urea, that such fall of urea is accompanied by a fall of acidity, and that the latter is the cause of an increasing collæmia.

The result of all these things is increasing collæmia, and collæmia produces defective circulation in the tissues and congestion of the liver, both of which are factors in the causation of diabetes.

Again, mental strain and anxiety at once raise the blood pressure, as we know by practical experience, from 20 to 30 mm. of mercury, and rise of blood pressure increases the backward pressure in the circulation and helps to congest the liver. Then mere anxiety or mental effort increases the flow of blood to the brain, often at the expense of the stomach, and may thus cause dyspepsia.

Thus mental anxiety and strain have a double action: (1) their direct effect in raising blood pressure and increasing venous congestion, and (2) their indirect effect through production of dyspepsia, which increases collæmia.

But these results are all dependent on the presence of excess of uric acid in the circulation, for in the absence of this neither shock nor anxiety could slow the circulation nor congest the liver to any appreciable extent.

There is said to be a connection between railway travelling and diabetes, and some have looked upon this as an effect of vibration, though how it acts they do not, I think, explain; but I think it is much more probably a result of the worry and anxiety involved, which produces in the way sketched out above rise of blood pressure with secondary heart failure and congestion of the liver.

And if this is so, we may expect to get presently a still larger crop among motorists, for with them the anxiety involved (at least in the case of the driver) must often be much greater than among

railway men and travellers; but motor drivers are generally younger men than guards and engine drivers, and the strain of high pressure would have less effect on the strong heart muscle of the young. Here we see quite clearly the real meaning of the common age relation of diabetes and glycosuria, for it is just in the decline of life that we get at once the greatest possibility of collæmia and that failing muscle power which makes it deadly.

In diabetes, just as in Bright's disease, heart weakness has an important influence in intensifying the effects of collæmia.

Cough is another thing which increases back pressure, and may thus give trouble to a weak heart and increase congestion of the liver; hence chronic bronchitis may, under certain conditions, become a factor in the precipitation of glycosuria or diabetes.

In suggesting that glycosuria and diabetes may be due to a failure of combustion and a slackening of metabolism, which, again, may result from the vascular effects of uric acid, pointed out in previous chapters, I am far from claiming that all such cases are due to uric acid.

I believe, however, that the connection between gout and diabetes is both wider and deeper than has hitherto been suspected; and that some of the riddles of this Sphinx (Frerichs "Ueber den Diabetes," p. 275) may be solved by admitting provisionally the power of uric acid over metabolism; and by thus admitting it provisionally, we are by no means bound to forego any opportunity that may offer of putting the point to the most careful test we can devise.

And the more careful and complete our tests the more evident will it become that glycæmia, glycosuria, and not a few cases of diabetes, are really due to a failure in the metabolism and combustion of carbohydrates, just as hetero-albuminæmia and albuminuria are due to a similar failure in the combustion of albumens, and that the action of uric acid on the circulation is sufficient to account for the failure of combustion in both cases, and so for the fact that both may occur in the same individual (see chapter xiii.).

Then, as pointed out in an article mentioned in the *British Medical Journal* Epitome, 1896, vol. ii., p. 97, and January, 1897, p. 5 of Epitome, there may be occasional excretions of a little sugar for years before there is true diabetes. And this is the exact parallel of what we see in migraine, when there is often occasional albuminuria for years before Bright's disease and constant albuminuria supervene; and as above mentioned, I have had under my care cases in which periodical migraine of many years' standing

has ended, not, as is usual, in albuminuria and Bright's disease, but in glycosuria and diabetes.

It seems, then, that there is here, between these two diseases, albuminuria and Bright's disease on the one hand, and glycosuria and diabetes on the other, an extensive parallelism — one might almost say identity ; and one cannot help feeling that, just as in the cases of headache and epilepsy previously mentioned, there must exist below this parallelism some community or identity of causation.

And this common factor, the cause of both diseases, is defective circulation, bringing about defective combustion, and we now see that the best and most complete explanation of the defective circulation is capillary obstruction by uric acid collæmia, which is to be seen in every case so caused.

There are also some indications that while the defective combustion thus produced may affect either albumens or sugars, or first one and then the other, its actual effect in any given case depends on associated conditions.

When the stress of the defective circulation, as determined by other concomitant conditions, such as cold and damp, falls on the skin, we are likely to get albuminuria and Bright's disease; and when it falls specially on the liver and chylopoietic viscera, then glycosuria and diabetes are more likely. And we see such a determining factor, perhaps, in the hernia from which W. H. suffered. In similar cases it might be well to operate on the hernia and free the intestines from any local irritation that may be the precipitating cause of dyspepsia, collæmia, and deficient combustion.

Cases which are still functional will respond most decidedly to the treatment of the uric acid factor; while those which have become organic, owing to changes in the metabolic tissues, will be affected only to a certain extent; and those which are from the beginning organic and due to lesions of the great nerve centres will hardly respond at all to the treatment of uric acid.

The indications for the treatment of such a glycosuria or diabetes are to diminish the introduction and formation of uric acid, and to clear out that which has accumulated in the body. A long course of salicylates will satisfy the last indication; and if they, at the same time, remove the sugar we ought, I think, to go gradually back to ordinary diet, and even beyond it; eventually reducing animal food to small quantities of milk and cheese; and unless we are able to do this I believe that relapse is merely a question of time.

As I have said, I believe that the large amount of meat commonly

given in diabetes acts as a stimulant, and therefore, just like opium or mercury, keeps the blood clear of uric acid for a time; but like these drugs it can only do good for a short time while the stimulation lasts, as it not only does not clear the uric acid out of the body, but, on the contrary (and in this respect it is worse than the above drugs), steadily pours into it a considerable quantity of this substance day by day.

Whether this great excess of uric acid has anything to do with the coma that often ends the disease may be doubtful, and I have already made some observations on this point, showing that, in the opinion of myself and others, the coma was due to inanition; but I am not at all sure, looking to the terrible effects of uric acid on nutrition and combustion, that the inanition in its turn may not be largely due to uric acid collæmia; and this would fit in very well with the fact I have observed, that a rise of urea which entails a corresponding rise of acidity generally suffices to clear off the inanition and the coma, for nothing clears the blood of uric acid like a rise of urea; nothing so certainly produces collæmia and a plus excretion of uric acid as a fall of urea. And I shall have to refer again in the following chapters to the evil effects of a pure meat diet when given for chronic arthritis, and in one of the cases there mentioned the patient was insensible for some thirty-six hours.

But be this as it may, I would make this practical suggestion, that the way out of diabetes is to clear the body and blood of uric acid, and that it is quite impossible to do this while an almost pure meat diet is pouring in the xanthins in large quantity every day.

The advantages of the use of salicylates in treatment have been pointed out by Dr. R. T. Williamson in the *British Medical Journal*, 1902, vol. ii., p. 1946. He there gives some interesting results of the effects produced by aspirin as compared with peppermint water, and his tables show very markedly the powerful effect of the salicylate in diminishing the sugar. He does not appear to consider that aspirin is better than salicylate of soda. From my experience I am inclined to think that aspirin is better; but if, as is sometimes the case, it upsets the stomach, then some other form of salicylate must be substituted.

More recently alkalies appear to have been used with very good results, and I see no reason why salicylate of soda, which acts as a solvent of uric acid, should succeed, while alkali, which is also a solvent, should fail. As I have previously said, small doses of alkali have often appeared to me to do harm, but very possibly the

error has been in giving small doses which were only sufficient to bring the uric acid into the blood and not sufficient to carry it out of the body. In many conditions due to uric acid it is necessary to give sufficient to get and keep the urine alkaline, or we shall not get good results, and it seems that this is the case in diabetes also.

The three things we have to do now stand out quite clearly: (1) To clear out uric acid by means of salicylates; (2) to maintain by every means in our power the nutrition and strength of the heart muscle; and (3) to introduce into the body no grain of uric acid or xanthin which we can leave outside.

I could easily give notes of further cases, but they do not show anything not also shown by the above cases.

And these demonstrate that in a considerable number of cases of diabetes, a course of salicylates, with the help of opium or calomel, will decidedly reduce the output of sugar, and check the progress of the disease, and that where they fail it is doubtful whether anything else will succeed.

Opium and codeina seem to me to labour under the fatal objection that they often interfere with appetite and cause a fall of urea as well as of sugar.

They cure also, if my pathology is correct, merely by clearing the blood of uric acid, and as no provision is made for its elimination, this is almost certain to be followed sooner or later by a rebound, with serious or fatal effects.

So far as I have been able to watch the use of opium and codeina by others, they have not presented any advantages over salicylates, and have appeared to me to fail in prolonging life as much as the salicylates might have been expected to do.

I have never cured a case of diabetes, but I believe that if cure is effected it will be by following the above indications.

W. H. died later on under my care, his disease having lasted more than four years.

In the intervals he had tried several hospitals and as many physicians, and he told me that nothing had done him so much good as salicylates with small quantities of opium or calomel.

When he returned to me the last time his case was quite hopeless, as he had wasted much during the last few months, and had bedsores, showing feeble nutrition; he had also some consolidation at the apex of one lung and a troublesome cough.

Here all drugs quite failed to produce an effect and, as in the corresponding stage of Bright's disease, the fires were so low and the tissues so wasted that it was impossible to stimulate them again.

Exercise may be useful in diabetes, as shown by a case mentioned in the *British Medical Journal*, 1899, vol. ii., p. 104. It must be regular, not spasmodic, for though exercise at first may increase collæmia, its steady daily use improves nutrition and diminishes collæmia.

Dr. S. West published in the *British Medical Journal*, August 24, 1895, his experiences of the treatment of diabetes mellitus by uranium nitrate, which he thinks may act by checking the rapid digestion of starch and some forms of albumen.

I have made a few experiments with this drug and the results show clearly the way in which it acts.

It causes a distinct rise of acidity and a diminished excretion of uric acid with well-being and diuresis, and these effects are so marked that quite small doses suffice to demonstrate them.

Thus on a day when no drugs were taken, urinary water was 1,520 cc., acidity 57·4 gr., and the relation of uric acid to urea 1—27.

On the following day gr. iii. of uranium nitrate were taken three times a day after meals.

This produced marked mental and bodily well-being, the urinary water rose to 1,860 cc., and the acidity to 61·2 gr., and the relation of uric acid to urea was 1—38.

I think, therefore, that nitrate of uranium clears the blood of uric acid and increases metabolism and combustion; and like many of the drugs mentioned above diminishes the excretion of sugar in diabetes, because it increases the combustion. I have had a patient under my care on uranium nitrate for more than eighteen months; she is a somewhat similar case to W. H., and is at present holding her own, though the dose of the drug has had (as one would expect) to be steadily increased; but this is obviously prolongation of life not cure.

Calcium is another drug which, taken in the form of powdered egg-shell, has been credited with curing or relieving diabetes, and from what has been said of the effects of calcium salts in chapter ii. it is clear that it may also, like the uranium salt, clear the blood of uric acid and improve combustion. I have also heard from Mr. Barker-Smith that he has known of one or two cases in which chalk has appeared to cure diabetes.

The facts above mentioned appear to me so strong, backed up as they now are by our power of estimating capillary circulation and combustion in all cases, and noting the effects of our drugs and treatment on these, that though I have not yet cured a case, I

have hopes that it may become possible to do so in the near future, for though small points in treatment still require adjustment, the main lines are clear enough. Then the power of control and cure which we now have in Bright's disease may be extended to diabetes.

These two diseases are so absolutely and completely parallel, both as to causation, circulation symptoms and reaction to treatment, that similar results in both are only a matter of time; and even to prolong life for several years in a case of severe diabetes is no small matter. The same case seen and recognised at an earlier stage might have been cured, and kept well on diet.

As regards the importance of diet in diabetes I may mention some reports I have had from Dr. A. Ghose, of Calcutta, where I understand that diabetes is a common disease, due, I suppose, to the large quantities of pulses eaten by the natives, and the effects of malaria, another consequence of pulse eating. Thus in a letter dated November, 1899, he says: "As regards your theory about diabetes it is perfectly true, and we do it here to the great satisfaction and prolongation of patient's life, though some physicians still stick to meat diet." And in a more recent letter he adds, "Now I am recommending all my diabetic patients a vegetarian diet," by which I understand that he means a diet free from pulses, as I had previously discussed with him the evil effect of these vegetables in the causation of rheumatism and stone.

Dr. G. S. Keith has recorded (*Lancet*, 1902, vol. i., p. 589) an interesting case of diabetes apparently cured by a restricted diet, and cutting down especially the quantity of nitrogenous foodstuffs. His records of the case are incomplete, but apparently both weight and strength were regained on the reduced food, and it seems to me that it is possible that in this case the diminished introduction of uric acid, together with some diminished formation, enabled the combustion to recover itself, and thus prevented the loss of unmetabolised sugar; and I certainly think this is worth trying in some similar cases, but this one was not very severe diabetes, as the highest specific gravity of the urine was only 1037.

The association of excess of uric acid in the urine with numerous granules in the blood, and of these with slow capillary circulation, high blood pressure, low surface temperature and anæmia, is constant; and my researches show that the uric acid is the cause, the other phenomena the results, just as Bright's disease and diabetes themselves are final or exaggerated results of defective combustion.

The returns of the Registrar-General seem to show that this disease, like others due to uric acid is a steadily increasing cause of

death from year to year as more and more meat is eaten. Bright's disease is only too often not recorded, and death is put down to cardiac failure or cerebral hæmorrhage, when Bright's disease was the real underlying condition. But diabetes is generally recorded as such, and not under the head of its complications or results.

This is no place for statistics or their discussion; but I would advise those who are interested to look at the figures of the last thirty years and judge for themselves.

The moment a man has a constant excess of uric acid in his urine, of granules in his blood, has defective capillary circulation and subnormal surface temperature, with or without high blood pressure, he is on the road to anæmia and Bright's disease, or diabetes or obesity, or a mixture of them all, in various proportions, as some other minor factors may from time to time determine.

But if by diet begun early in life you control the uric acid and with it the capillary circulation, and will measure and watch the latter, and see that your control is real and effective, the above diseases, in spite of their different names with their long and respectable history, will often prove that they are incidents of defective combustion by departing in considerable haste and confusion to those desolate regions where stimulant poisons like uric acid, xanthin, thein, caffein and meat extracts are still regarded as foods.

I have seen several cases in which small quantities of sugar have promptly disappeared from the urine when the patients were put on the uric-acid-free diet, no attention whatever being paid to the quantity of carbohydrates. In some cases where this occurred I was disposed to think that the substance in the urine had possibly not been sugar at all, but rather excess of uric acid or creatinin. But in one case I know of this was not so, for a few years later the same patient, who did not keep up the uric-acid-free diet, got more distinct glycosuria, and in another case when I sent the urine to Messrs. Savory and Moore for investigation I was assured that the substance present was glucose to the extent of 2·2 gr. to the ounce. I must conclude, therefore, that these were very slight cases of defective metabolism, and that the change of diet came in time to improve the capillary circulation and relieve the heart and liver in the way we have discussed in the previous part of this chapter, and thus the small amount of glucose which was passing into the urine took its departure in the course of a few weeks. So far as I know these cases remain well if they keep on the diet, but if they do not do so they may relapse, and then the sugar will probably increase, this being the exact parallel of what occurs in slight cases of albuminuria.

CHAPTER XV.

Gout.

Since I discovered that in driving uric acid out of the blood while curing an attack of headache or mental depression I produced pricking and shooting pains in the joints, the explanation of the arthritis of gout has never seemed to me to be a very difficult matter.

And when we have obtained a complete knowledge of the chemistry and solubility of uric acid under the conditions present in the human body, we shall have no difficulty in explaining completely the phenomena of gout.

I am quite prepared to undertake to produce a uric acid arthritis in anyone, provided my instructions are carried out, but the clinical result will often resemble what is described as the arthritis of rheumatism rather than that of gout.

From my point of view the arthritis in both diseases is due to uric acid, which, in acute rheumatism, is suddenly driven into a large number of joints, where, however, it remains generally only for a short time, and is then more or less completely removed; but in gout a great part of the uric acid in the blood is (generally by the action of some external causes) concentrated on one particular joint, where it is not only present in greater quantity, but remains longer than in the case of acute rheumatism.

I believe, however, that it is possible by imitating nature to produce at pleasure an arthritis which would be called rheumatism, or gout, by those who did not know how it was produced.

If, in the arthritis called rheumatism, the uric acid is removed in the course of a few days, only microscopic lesions are produced, which are quickly repaired, and leave no trace after death, but if injury, cold, or other external causes prevent the removal of the urates from one or more of the joints, they may set up and maintain an irritation in its fibrous structures which may obtain a con-

siderable hold on the tissues, and, causing in them a marked lowering of alkalinity, bring about the retention of further uric acid in the same place, either attracted by the uric acid already there (uric acid filter action) or retained because of the diminished alkalinity; and so the local trouble enlarges and extends so long as there is excess of uric acid in the body and blood. In this way are brought about extensive lesions of structure which, even after acute rhumatism, are sometimes visible after death, and where uric acid has been again and again precipitated (from causes I shall presently speak of) on the irritated areas, or where these areas are constantly bathed in a blood rich in urates, changes commonly called rheumatoid are produced.

These rheumatoid changes, when extensive, should be regarded as in part the direct effects of the irritant uric acid, and in part due to the smouldering on of the irritation it causes, so that I have been accustomed to speak of the uric acid as the fire and the rheumatoid changes as the ruins, and obviously the treatment of the ruins is a very different matter from that of the fire. To remove the uric acid is the best treatment of the fire, but that will not rebuild the ruins.

I was interested to see that in his address in the Section for Diseases of Children at Bournemouth, Dr. Goodhart speaks strongly as to the relationship of gout and rheumatism. Thus (*British Medical Journal*, 1891, vol. ii., p. 252) he is reported as saying: "In the first place I hold that gout in children is not to be discriminated from acute rheumatism"; and further on he says: "I think in summing up what gout is we must say that under some circumstances, or at one period of its life, gout is acute rheumatism."

I have shown that under all circumstances and at all periods gout is rheumatism and rheumatism gout, and that while both are due to uric acid the clinical picture varies with age and other factors, the action of which can be completely explained.

Again, I note that Mr. Jonathan Hutchinson says (*Trans. of International Med. Cong.*, 1881, p. 92) that rheumatism and gout occur in the same families, and the one is as much hereditary as the other; and he also says, "Thousands of specimens will be found in museums showing rheumatism only, but of those which show gout (lithate deposits) there are but few which do not show some traces of the changes characteristic of rheumatism" (p. 96); and on the same page he remarks that "rheumatoid arthritis is seen in children as the result of descent from gouty parents; also

a special form of iritis, especially seen in those who inherit also proneness to chilblains." There is no lithate deposit in such cases, but later on, especially if disease of kidneys comes on, then they get urate deposit.

It is necessary to make these preliminary remarks, or the position I take in this and the following chapter would not be understood.

And this position is: that much arthritis and many irritations in other fibrous tissues are the direct local irritant effects of uric acid, which effects tend to come on and increase under conditions which hinder the solubility of uric acid and tend to diminish and get better under conditions which favour its solution and removal; that the ultimate results depend upon the reaction of the individual and his tissues to the irritant, and that this will vary with growth, development, time of life, state of nutrition, and other minor concomitant conditions.

In a word, any arthritis which does not react and has not reacted to conditions which would certainly affect the solubility of uric acid is probably not due to it, and only ignorance of these conditions has prevented this from being obvious long ago.

What evidence have we that uric acid produces such irritation as that I am speaking of in the fibrous structures?

I have often quoted Sir A. Garrod's remarks on the effects of wines, &c., and have suggested that it was the acid in these beverages that drove the urate into the joint and produced the inflammation, of which the pricking pain is the sign; he says (p. 245), "Where a few glasses of wine, ale, or porter quickly and invariably produce in any individual an inflammatory affection of a joint, such inflammation is of a truly gouty character"; and in the lines preceding this he mentions how some sufferers have heat, throbbing, stiffness, and pain in their gouty joint after two glasses of port or a single glass of champagne. Now it is easy to demonstrate that champagne is intensely acid—more so than the other wines and malt liquors mentioned, and Sir T. Lauder Brunton, in the debate on my paper on "Salicylates and Rheumatism" (*Proceedings of the Royal Medical and Chirurgical Society*, April, 1890, p. 109), mentioned a case in which champagne had apparently produced symptoms of poisoning by its great acidity.

This time observation of Sir A. Garrod's furnishes also a strong argument against the idea that the cause of the irritation in joints and fibrous tissues is the precipitation of needles of biurate, for the late Sir W. Roberts shows ("Croonian Lectures," 1892, p. 97) that

in solutions of a strength at all likely to be met with in the human body, the biurate does not begin to be thrown down even in glass for more than thirty-three hours, and in the living tissues it is hardly likely to deposit more quickly than in glass, while Sir A. Garrod tells us (previous reference) that wines may produce gout "quickly"—"before quitting the dinner table."

We have evidence that urate in solution produces irritation, while almost every student knows that in the *post-mortem* room biurate deposits may be found in joints without any recent history of pain in them, and without any sign of recent inflammation in surrounding structures. And Magnus-Levy found uric acid in the fluids of an acutely gouty joint, but no crystals. See also Drs. E. Schreiber and Zandy (*Archiv. für die ges. Physiologie*, Bd. 79, S. 97), who also give other reasons for believing in the toxicity of uric acid.

There can, then, be no doubt that these beverages acted as doses of acid more or less strong, and drove the uric acid out of the blood into the already irritated joint, and for the effects of sherry on the acidity of the urine see fig. 63; but all these things can be easily shown to affect, not only the acidity of the urine, but the excretion of uric acid and the condition of the blood itself, as shown in fig. 52.

Then, as mentioned by the late Sir W. Roberts, in the above debate, Ebstein has shown that urate dissolved in phosphate of soda produces irritation and morbid change when injected into the cornea, while the phosphate alone produces none.

Again, Sir A. Garrod has pointed out (previous reference, p. 292) that the cartilages and fibrous tissues of joints have but little vascularity and are less alkaline than other tissues, or than the blood, and if this is so we can easily see why urates should become "less soluble and more easily retained" (to quote Sir A. Garrod's words) in the neighbourhood of joints.

Further, the joints in the old are probably both less vascular and less alkaline than those of the young, so that such external causes as injury or cold will more easily diminish their alkalinity in the old and produce a local concentration of urate and a gouty arthritis.

In the young, on the other hand, the effects of local cold or injury will be less, the alkalinity will be better maintained, and it will only be when general causes act all over the body, such as severe chill and wetting during perspiration, that the alkalinity of all the joints will be reduced at once, and the more general arthritis of acute rheumatism will result. Hence the joint irritation pro-

duced by urates tends to be general and acute in the young (acute rheumatism), local and subacute or chronic in the old (gout).

With regard to the action of acids, I have produced pricking and shooting pains in my own joints many scores of times, when using them to remove the uric acid headache or mental depression (see also remarks on fig. 63), and in a case of gout under the care of Sir Dyce Duckworth in St. Bartholomew's Hospital, where he kindly allowed me to examine the urine, I was able to show (*St. Bart. Hosp. Reports*, vol. xxiv., p. 217) that every time the acidity rose the uric acid fell below the urea (relation 1—45 or 1—50, a great retention of uric acid), the temperature tended upwards and the pains increased and became severe, and conversely, whenever the uric acid was above urea (relation 1—24, excretion in excess of formation)—whether this result was produced by salicylates or alkalies—the pains diminished or ceased, and the temperature subsided.

As back numbers of *St. Bartholomew's Hospital Reports* are not very widely available I reproduce one of the figures of the above paper as fig. 62.

From this we see that on May 27, with a high rise of acidity, uric acid was below urea and temperature at night was 101·6° F.

On 29th with a fall of acidity uric acid was close to urea, and the evening temperature only rose to 99·6° F.

On 30th and 31st with rising urea and acidity there is some increased retention of uric acid, and the evening temperatures reach 99·8° F. and 100·2° F. respectively.

On the 1st and 2nd of June the uric acid is rather nearer urea and the temperature is more steady and below 100° F. all day.

On the 3rd, 4th, and 5th, again, with rising urea and acidity uric acid is again retained, and the evening temperature rises on the 3rd and 4th to 101° F. and 101·2° F. respectively.

On the 5th, however, as the pains were bad salicylate of soda was given in the dose of gr. xv. four times a day, and this came in time to relieve the pain, which it did, as the patient said, soon after the first dose, and to keep down the temperature on the evening of the 5th to 99·8° F.

On the 6th uric acid was considerably nearer urea, and the temperature again only reached 99·8° F., and on the 7th the uric acid was 3½ gr. above urea, and the temperature only reached normal in the evening, and in the following days fell below it, the irritant urate having for the most part been removed from the tissues.

But few words are required to emphasise the very constant relation here seen between retained uric acid and rising temperature (and with the temperature there was always pain), and excreted uric acid, relief of pain and falling temperature.

No doubt the temperature at the beginning of the figure was due to some retention which we do not see before it, and this was merely reinforced by the retention on 27th.

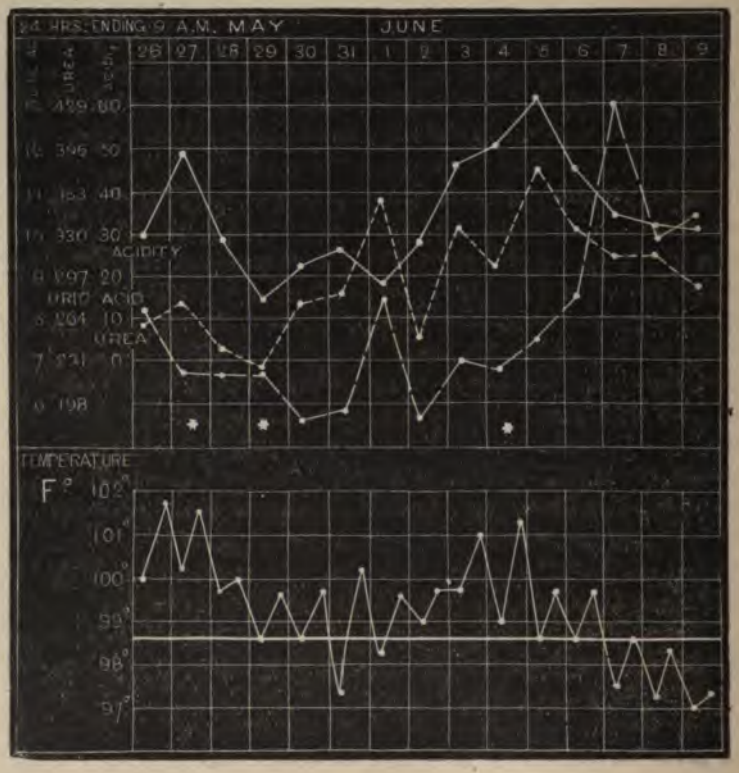

FIG. 62.—CURVES OF THE EXCRETION OF URIC ACID IN GOUT AS PUBLISHED IN *St. Bartholomew's Hospital Reports*, 1888.

For the rest, considering that probably no collection of urine or estimation of uric acid ensures absolute accuracy, the correspondence is remarkable. The same may now be demonstrated more directly by estimating the granules in the blood.

I hope that anyone who is still sceptical about the effects of acids in gout will look at the curves given in fig. 62, and will then

try acids on themselves, or any gouty patient who will consent to the experiment, and I am confident that the results will remove all doubt. For a similar observation in an attack of gout, see clinical note by Dr. Lyddell, *Lancet*, 1893, vol. ii., p. 631.

For other figures, which all show the same thing, that temperature rises with low uric acid and falls as salicylates produce a plus excretion, I must refer to my original paper.

These results were obtained in 1888, and with the much, but very unjustly, abused Haycraft's process, and I have therefore been interested to see that a more recent observer, Dr. Chalmers Watson, working with a different process, has obtained identical results, which he published in the *British Medical Journal*, 1900, vol. i., p. 10, and in the table I. on p. 12 we see the following figures:—

On May 31 the patient was put on pot. iod. and sodii salicyl. āā gr. x., and with this we get relatively small excretions of uric acid and large excretions of urinary water, for naturally the retentive action of the large dose of iodide would overcome the excretive action of the small dose of salicylate, and the water as usual moved in the opposite direction to the uric acid.

On June 13 these drugs were discontinued and the patient was left without any, being on a mixed diet; and what I have spoken of as a rebound then took place, the uric acid increasing and the water diminishing, and with this no doubt there was considerable collæmia with slow capillary reflux, raised blood pressure and its results.

The lowest water was 936 cc. On 16th and 17th, however, the uric acid diminished in relation to urea, the water ran up to 1,515 cc., and with this the temperature rose for a few hours just above normal, having been below 98° F. with the large excretion of uric acid and the low water on the 16th.

It will be noted how, when we have the key, all the facts fall into place. I could not possibly have produced better results to illustrate the laws I have expounded in the previous chapters than these figures of Dr. Watson's.

On the 18th uric acid again rises in relation to urea, and water falls to 1,015 cc., and, with this, temperature is not above normal on the evening of the 17th.

On the 19th uric acid again falls in relation to urea, water rises to 1,285 cc., and temperature on evening of 18th reaches 99·6° F.

On the 20th uric acid falls still more markedly in relation to urea, the water rises to 1,440 cc., and the temperature rises on the evening of 19th to 101° F.

With this we are told that the pains reached their maximum in the early morning of 20th, and in that day either two or three doses of sodii sal. gr. xx. were given,* and the very acute pain disappeared on the afternoon of 20th.

The urine of the 20th also showed a very marked rise of urea which then reached the highest level in the table, and this no doubt was the result of the free capillaries and active combustion of the evening of the 19th, when the blood was nearly cleared of uric acid, and when, had it been examined, but few granules would have been found.

And now see the effect of the salicylate; the uric acid rose greatly in relation to urea, the water fell to 775 cc., the lowest excretion in the whole table, the pains were relieved on the night of 20th, and the temperature fell next morning to 97·6° F., the lowest temperature in the chart, this coinciding with the largest amount of uric acid in the blood and the greatest number of granules in the blood (see previous records of Effects of Salicylates on Blood Granules, chapter iii.).

The uric acid maintained a relatively high position on the 22nd also and the water only rose to 815 cc., so that the salicylate no doubt continued in action part of the following day; and though the temperature in the morning was not so low and the uric acid in the blood less, it is evident that the drug had cleared out most of the urate and broken the back of the attack.

Almost every law I have propounded is illustrated in this table: how with high uric acid we get low water, low or falling urea, and low or falling temperature; all corresponding no doubt with the skin sign of collæmia—a slow capillary reflux.

On the other hand, with low uric acid we have high urinary water, high or rising urea, high or rising temperature, again no doubt corresponding with the skin sign of absence of collæmia—a quick capillary reflux.

And we have produced all these changes ourselves, and know exactly how we produced them in the cases of Bright's disease and diabetes recorded in previous chapters. There as here, as the blood was cleared of uric acid and the combustion improved, the temperature rose from subnormal to normal or slightly above it.

Indeed, I may say that I believe the normal temperature of a person who is as free as possible from uric acid collæmia is above 98·4° F. and more like 98·8° F.

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* In the table we are told that it was given twice, but in the notes below it three doses are mentioned, at 12.15, 5.30 and 8.30 p.m.

Those who refer to Dr. Watson's table from which I have been quoting will find the figures of the relation of uric acid to urea do not correspond with those in this book. His lowest uric acid is 1 to 76, and his highest 1 to 32. My lowest is above 1—50, and my highest 1—15 (*i.e.*, in the patient whose gout attacks are recorded in fig. 62).

The difference is due to the different process used for the estimation of uric acid; Dr. Watson might say that Haycraft's process estimates uric acid too high, and I might reply that the process he used estimates it too low; but when this had been said we should not be any better off; and what I want to point out here is: that the large and important fluctuations of uric acid come out quite clearly with almost any of the processes now in use, and that for that matter I could have told nearly everything that happened to this patient from the excretion of water alone; that I could have told the water from the temperature, or the temperature from the water, and the uric acid from either; and that so far from its now being necessary to use elaborate processes for the estimation of uric acid, anyone who is provided with a thermometer, or even with the point of his finger and the second hand of his watch, can tell correctly all the chief fluctuations in urate excretion recorded in this table.

The capillary reflux is a satisfactory guide to the quantity of uric acid in the blood, or the blood itself can easily be drawn and examined; so that for clinical work it is rarely or never necessary to wait for the collection and estimation of the uric acid in the urine.

Some of Dr. Watson's conclusions scarcely seem to me to be in accordance with his facts.

Thus he says (previous reference, p. 14): "The alkalinity of the blood is not diminished during the attack," which is probably equivalent to saying the acidity of the urine is not increased during the attack.

But in fig. 62 the acidity of the urine is high or rising each time the temperature rises, and in Dr. Watson's table the excretion of P_2O_5 is stated as 3·144 grains on the day that uric acid is relatively low, corresponding to the temperature of 101° F. on June 19; on the previous day the P_2O_5 was only 1·745 grains.

Then he says, "The excretion of uric acid is not diminished by the attack, but the reverse." The only ground for this statement, which is diametrically opposed to my results, and also as it seems to me to his own, is that Dr. Watson appears to date the attack in his patient from June 17, when there was a slight rise of tempera-

ture in the morning, but it was again subnormal in the evening; whereas the real attack and the great rise of acidity and diminished excretion of uric acid were not til the evening of the 19th, and everything corresponds with this, namely, the rise in urinary water, urea and temperature, as already pointed out.

Then in fig. 62 we see that the further uric acid falls below urea the higher is the temperature; the absolute height of uric acid has but little to do with it, though it is always far lower absolutely in the attack than when salicylate cures it.

His last conclusion is, "The amount of uric acid in the blood is not greater during the attack than in the intervening period." With this I quite agree, but it is an under-statement of the facts, for there is far less uric acid in the blood during the attack than before and after it.

This is shown by the excretion of uric acid in the urine which Dr. Watson gives; it is shown by the temperature during and after the acute pain; it is shown by the urinary water, and it would certainly have been shown by the capillary reflux and the blood granules had they been examined.

In fig. 62 it is shown by the relation of uric acid to urea at the time of the raised and subnormal temperatures respectively, and in Dr. Watson's chart the lowest temperature of all was clearly due to the excess of uric acid in the blood which the salicylate occasioned.

As I can only admit one of his three conclusions, I cannot of course follow his final point which is dependent upon them when he says: "If these points be accepted, we must start *de novo* in search of the cause of the acute paroxysm."

To my mind the cause has been staring me in the face these twelve years, since 1888, when I got the results shown in fig. 62, and it seems as I have said, to be just as clearly visible in Dr. Watson's figures as in mine.

Let those who wish start *de novo* as much as they please, but meanwhile I have absolute power either to produce or relieve the acute paroxysm, and by means of the water, urea, temperature, capillary reflux, and blood granules, can watch every change as I produce it.

In Dr. Watson's case the attack was due to the uric acid introduced in mixed diet or thymus; but the idea of watching the effect of feeding thymus, while keeping on a drug like iodide, that prevented solution and excretion, is rather original, and no possible conclusion could be drawn as to the amount of uric acid or xanthin in the thymus.

When the iodide was left off, the uric acid previously stored rushed into the blood, lowering the excretion of water, and producing on June 15 and 16 a subnormal temperature. While this was the state of affairs, some acids or acid-forming food in the mixed diet ran up the acidity of the urine (as we see), diminished the alkalinity of the blood and its solvent powers for uric acid, and the urate being driven into a joint, the rise of temperature, the pain and the diuresis were the natural results.

I have produced and seen the production of scores and scores of identical results, and my general laws suffice to explain every fact in the record.

Dr. Watson has since published a paper, *British Medical Journal*, 1905, vol. i., p. 127, on "Reasons for Abandoning the Uric Acid Theory of Gout," but I must say that his somewhat sweeping general conclusions appear to me to be as little justified by the facts brought forward as those I have criticised above. Several of his points have been completely explained in the preceding chapters, and there is one which he, in common with other observers, has really never attempted to face, namely, that by reducing the uric acid output to one half of its original quantity, gout and all its manifestations, both local and collæmic, can certainly be removed; and that, when this has been done, all the symptoms can be brought back simply by once more resuming either the uric-acid-containing foods, or by swallowing known quantities of pure uric acid or xanthin. The cure of gout by uric-acid-free diet reduces the uric acid output from some 20 or 22 gr. a day to 10 or 11, and this can be done without any alteration of nutrition, without any fall in acidity or urea, without the production of any debility or anæmia, but, on the contrary, with advantage in all these directions, with increased strength and power of endurance, with normal temperature and improved blood quality. It is clear, then, that in this experiment nothing except the uric acid need be altered; the uric acid being taken away, all its effects disappear, the uric acid being put back, all its effects return. I am claiming nothing as the result of uric acid, which cannot be produced or removed by giving or withholding this poison. The causation of gout by uric acid is not a theory but a fact. The so-called uric acid diathesis, the belief that some people form more uric acid than others, the belief that uric acid is the result of deficient oxidation instead of its cause, is a mere theory without any solid foundation whatever, and it may be demonstrated that collæmia on the one hand, or arthritis on the other, originate by mere administration of pure uric acid. Let those who assert that

uric acid is not poisonous undertake to swallow 6 gr. of it every day for a month, and if by that time they have not suffered sufficiently from collæmic troubles, let them take a small dose of salicylate of soda, followed by a Turkish bath, and if that does not convince them they must, so far as I am concerned, remain unconvinced, though I will take no responsibility should this produce serious results. When the quantity of uric acid in the blood can be observed from hour to hour, and its effects on the capillary circulation measured with accuracy, when the blood can be examined from hour to hour and the quantity it contains demonstrated, and when, by the administration of pure uric acid this quantity can be increased or diminished at will, and it can be shown that all its effects increase or diminish also, it is, in my opinion, waste of time to talk about the causation of disease (either arthritis or collæmia) by uric acid as a theory. It is a fact, and one which anybody who has a taste for clinical investigation can demonstrate for themselves in a few hours.

If it were true that certain people through defective oxidation could produce uric acid out of foods which those with better oxidation do not produce it out of, it would be impossible to cure such people of their gout or of their collæmia by merely withholding uric-acid-containing foods; and in spite of the uric acid introduction having been cut down 10 or 11 gr. a day, such people would still form excess of uric acid and still suffer from collæmia, and occasionally also from arthritis. As a matter of fact this is not the case, and all who take the trouble to reduce their uric acid ingestion will gradually become free from disease.

In reference to physiological relations I would point out that the attack of gout commonly occurs at night during the acid tide, when the excretion of uric acid is at its lowest, and during the course of the attack the pains are always worst and the temperature highest at night. The curves in my paper above referred to show this well. Sir A. Garrod (previous reference, p. 42) quotes from Sydenham's description of the attack in which the hour of onset is mentioned as 2 a.m., and on p. 44, still quoting from the same authority, we find this statement: "One thing, however, is constant—the pain increases at night and abates in the morning." I hope no one who has followed my reasoning will have any difficulty in understanding the meaning of this. It is in absolute accord with my statement, that the excretion of uric acid is inversely as the acidity, and that when uric acid fails to be excreted, it is retained in the joints and irritate them.

As regards season, Sydenham's account is equally emphatic. He says (p. 42): "Towards the end of January or the beginning of February suddenly and with scarcely any premonitory feelings the disease breaks out." That is to say, at the very coldest season of the whole year, when the acidity is highest and the excretion of uric acid least (see fig. 4).

But indeed, the whole of Sydenham's description can be easily explained in terms of uric acid excretion by anyone who is conversant with it. Thus he says (same reference, p. 42): "But a few days before this (that is, the attack) torpor comes on and a feeling of flatus along the legs and thighs." This means a slight fall in acidity (no doubt due to the stomach derangement he speaks of as a forerunner of the attack), a plus excretion of uric acid, and its excess in the blood causing "torpor," or, as I have described it, mental, metabolic and general depression (see also previous remarks on Dr. Watson's case). Then see what happens; he goes on: "Besides this there is a spasmodic affection, whilst the day before the fit the appetite is unnaturally hearty. The victim goes to bed in good health and sleeps," and at 2 a.m. is roused by the pain.

We have seen that there was dyspepsia with fall of acidity and collæmia with "torpor" as its sign. Then the stomach improves; "the appetite is unnaturally hearty." Up go urea and acidity at a time when the blood is highly charged with uric acid, with the natural result that it is driven into the joints, and this occurs at an hour when the acidity has been rising for some time and is nearly at its highest point.

We can now see our factors quite clearly, almost as well as if we had produced the attack ourselves. (1) Dyspepsia producing a fall of acidity and collæmia. (2) Improvement of digestion and appetite raising acidity and driving the uric acid out of the blood into the joints. Can anything be more simple? and this sequence can be imitated at pleasure to any extent. But it is only by acting on a natural or artificially produced collæmia that arthritis can be caused; when there is almost no uric acid in the blood we cannot drive it into the joints: hence as we shall see all treatments by drugs, salts (sulphates, &c.), mineral waters, or pure meat diet, which stimulate nutrition and combustion and keep the blood free of uric acid for a time, do for such time also keep off arthritis. Conversely the worst conditions for chronic arthritis are those where joints are already irritated, and a constant supply of urates in the blood keeps up the irritation.

With regard to pure meat diet, all uric acid absorbed in the

intestines has to pass the liver, and, as we have seen, a large nitrogenous metabolism means high acidity of the liver, and high acidity of the liver means retention of every grain of uric acid that comes to it (see uric acid filter experiments, chapter v.).

Thus, in spite of large introduction, a pure meat diet keeps the blood clear of uric acid, and so long as it does so arthritis cannot be produced.

The moment that stimulation and acidity fail, however, the acidity of the liver falls, and then there is a correspondingly large rush of uric acid into the general circulation, and this is no doubt what occurs when morphine, mercury, iodides and other retentive drugs are suspended.

In connection with this causation of arthritis, I was much interested to hear Dr. Oliver, of Harrogate, say at a meeting of the British Balneological and Climatological Society in April, 1896, that in olden times he had often seen gout flare up in patients coming to Harrogate, as it was then the custom to put them in hot immersion baths, and these seemed to develop the gout attacks: and I hear from Dr. D'Oyly Grange, of Harrogate, that some patients still have acute gout on first coming there, and this is, no doubt, due to the salts and sulphur in the Harrogate water; but if a gouty patient is put into a hot bath, which, acting like the Turkish bath (in fig. 72), floods his blood with uric acid, then the Harrogate water will be almost certain to produce an attack of gout.

Why does gout come in January and February? (1) Because during part of November, the whole of December, and January the weather is cold. This diminishes the excretion of acids in perspiration, and keeps the acidity of the urine high (Sir A. Garrod) and the alkalinity of the blood low; hence, during this period, the excretion of uric acid falls short of formation and introduction, and it is retained and accumulated in the body, the opposite condition to mental depression, and at the opposite end of the year (see fig. 4). (2) When, at the end of January, dyspepsia lowers acidity for a day or two, there is a large store of uric acid in the body which is washed out into the blood, producing collæmia with "torpor" as its sign. (3) On this supervenes a sharp rise of acidity which quickly clears the blood of uric acid, driving it into the joints. (4) During the "good health" of the day before the attack the patient has probably taken a little extra exercise as well as a little extra food, and during the exercise he has produced a little warmth and diminished alkalinity in some of the joints of his feet.

This has not subsided when the rising acidity of night not only prevents its fall, but increases it. Hence, at 2 a.m., certain joints in the feet are the least alkaline structures in the body, and most of the uric acid in the blood is concentrated upon them, a uric acid filter is set up, and acute pain and inflammation result. The whole thing is a fluctuation in the excretion of uric acid, which can be imitated to any extent.

A gout attack can be produced by acids or any drugs which directly or indirectly raise the acidity or otherwise interfere with the solubility of uric acid.

But these drugs will not produce an attack unless there is plenty of uric acid in the blood for them to act upon, so that the mere fact that an acid or a dose of mercury, nux vomica, &c., has been taken without producing any pain proves nothing.

If you are going to produce an experimental arthritis you must first bring a quantity of uric acid into the blood in solution probably with a salt of potash or soda, and then administer some of the drugs which will interfere with its solubility and drive it into the joints and fibrous tissues; this is what occurs in nature, otherwise an attack of gout or rheumatism does not result. A rise of acidity or the taking of a drug which causes retention when the blood is nearly free from uric acid naturally produces no result.

From what has been said, it must be obvious that an acid may fail to produce an attack of gout for several reasons. (1) It may fail to be absorbed from gastric irritability (nausea, vomiting, &c.), or it may irritate the stomach, and prevent its own absorption and that of food also, and so lower rather than raise acidity. It is specially likely to do this when given too concentrated, or in too large a quantity at one time. (2) When absorbed it may be overpowered by alkaline salts of potash or soda present or produced from other sources (as debility, perspiration, &c.). It is always necessary, therefore, to see that an acid given raises the acidity of the urine. (3) There may be no uric acid in the blood owing to its previous removal by a course of salicylates or other solvents, and then there is obviously nothing for the acid to act on, and no gout results.

I notice that Dr. Luff in his Goulstonian Lectures (*Lancet*, i., 1897, p. 1070) objects to my statement that diminished alkalinity of the blood causes retention of uric acid in certain tissues, and he then goes on to speak of the solubilities of sodium biurate. But why trouble about sodium biurate? I should acknowledge that the uric acid if long retained may eventually become sodium biurate,

but we have to deal with it at the time it is in the blood, when according to the late Sir W. Roberts it is a quadriurate; for acids diminish and alkalies increase the excretion of uric acid in the urine from hour to hour, almost from moment to moment, and the presence of more or less irritation in some fibrous tissue is a frequent concomitant of the diminished excretion; but here we are dealing with uric acid as it is in the blood and tissue fluids, and that it eventually becomes a biurate when deposited in the tissues is a matter of no consequence.

All the uric acid with which I am concerned in this book probably exists as uric acid or a quadriurate either in solution or in colloid form; and only in this and the next chapter have I to deal at all with the biurate of sodium, and that only *after* the arthritic irritation has been produced. For we often see the biurate plastered over joints and not causing an atom of irritation (see also my reference to Pfeiffer's experiments on himself in chapter xvi.). When uric acid is being retained in the body by the action of an acid it is as a spherical or colloid urate, but still in suspension and non-crystalline. And when uric acid is being excreted in excess as the result of taking an alkali, this alkali meets with it in the blood or tissues, probably as uric acid or a quadriurate (see Mordhorst's results quoted in chapter v.).

Now, the late Sir W. Roberts tells us ("Uric Acid, Gravel, and Gout," p. 86) that the acid urate of sodium is not thrown down from a solution of quadriurate in serum till the second or third day, and it seems probable that in the living tissue fluids it will take even longer.

But Sir A. Garrod tells us in the passage already quoted above, that "a few glasses of wine, ale or porter quickly—produce," &c., and we see in fig. 66 that the arthritic pains were very marked within an hour after swallowing the dose of acid; obviously then the arthritis could not be due to deposition of the biurate, but was probably due to retention of uric acid either in solution or more probably in colloid form, and this is what I have been suggesting for years past in previous editions, not deposition, but *retention*.

And if this is correct we have here probably one rather important difference between the arthritis of gout and that of acute rheumatism.

In acute rheumatism the arthritis is often only a matter of a few hours, for even if it continues, the irritation may leave one joint and go to another, proving that the urate is soluble and can be moved from place to place. And this alone is a powerful argument against

Dr. Luff's contention that the biurate is the cause of the irritation in gout; for in gout we have the biurate deposited without any sign of irritation round it, and in rheumatism we have very severe irritation without any biurate deposit, or time for it to be deposited.

And this is almost certainly due to something more soluble than the biurate, which has not had time to be deposited: hence in acute rheumatism there is but a passing inflammation similar to that in gout of the fibrous tissues, as described in chapters xvi. and xvii. and in fig. 74; and here the soluble urate is all taken up again into the circulation, and leaves little or no deposit of acid urate behind it (see also chapter ix.).

In gout, on the other hand, the urate is not only present in greater quantity in the one joint affected, but it remains longer, and so the biurate is deposited, and this may go on for some time attracting other urates to it as long as the blood is rich in urates, so that the tophus grows steadily larger.

Here we have undoubtedly to deal with the biurate, and must consider its solubility in any attempt we may make to dissolve and remove it.

But here again the chemical facts are not nearly so difficult to reconcile with clinical experiences as some appear to believe.

Thus the late Sir W. Roberts tells us that the biurate is not entirely insoluble in blood serum, and again he says (previous reference, p. 108): "The solvent relation of the bodily fluids to the material of gouty deposits is simply a question of saturation or subsaturation. If the lymph or synovia at a certain spot became saturated, or rather supersaturated, with sodium biurate, precipitation of that substance will inevitably take place into the contiguous fibrous tissues. And if after such an event the lymph or synovia recover their purity and become approximately free from biurate, as in due course usually comes about, a process of slow resolution will of necessity set in.

Now this is very interesting, and it explains a clinical experience of mine that one often appears to get more benefit, as regards the clearing up of old gouty troubles, from several short courses of salicylates with pauses between them, than from a single long course; and each time one starts fresh, one gets a large excretion of uric acid, though towards the end of the previous course it had been but little increased.

And the results given in my curves show that the effect of leaving off salicylates after some days' administration, is a great fall in the excretion of uric acid in the urine, which is thus for

some days below its normal relation to urea, and it seems probable that during these days the lymph is in a condition of subsaturation, and some resolution of biurate deposits consequently occurs.

Again, and this is a matter of the greatest interest, Sir W. Roberts shows (previous reference, pp. 79 and 80) in his experiments, that the biurate is comparatively soluble in water, and that the solvent power of serum or a saline solution increases as the percentage of saline it contains diminishes.

It follows that a blood which is watery and poor in salines, is a much better solvent of biurate deposits than a blood which is concentrated and rich in salines.

And this is exactly what we find in nature, for as I have been pointing out over and over again in the previous chapters (see chapter vi. and elsewhere), it is in the old, feeble, debilitated and waterlogged that we get a constant excess of uric acid in the urine, and what appears to be a comparatively rapid removal of biurate deposits from gouty joints, leaving little but erosion to mark the place where they were.

Now, as we have seen in previous chapters, the presence of an excess of uric acid in the blood makes it dilute and watery by diminishing the outflow of water from the kidneys, so that we get in chlorosis, as Dr. Jones has pointed out (see chapter xii.), not only a lowering of the blood decimal but a fall in the specific gravity of the blood.

And the same in Bright's disease, when there is retention of water and dropsy, the blood (as in the case examined in chapter xiii., for instance) is poor and watery, and contains but a low percentage both of hæmoglobin and cells.

And this is not all, for in conditions of weakness, debility and emaciation we get low nutrition and slackening of digestion and metabolism in general, and as a result, very low excretion of urea per pound of body weight.

But the urea is the index of the breaking up of albumins and albuminous tissues, and while the nitrogenous portion of these goes to produce this urea, their salts and acid-forming radicles no doubt furnish the corresponding saline constituents of the blood and urine, and hence, as I have shown, the acidity of the urine varies up and down with the urea.

Therefore, in conditions of debility, wasting, and especially if there is dropsy, we have two very powerful conditions tending to make the blood and its serum watery and poor in salines, and this will, as we have seen, directly increase their power of dissolving biurate deposits.

Again, it is not to the point with regard to the large excretion of uric acid in the urine produced by the administration of alkalies or the diminished excretion produced by acids and acid salts, &c., to show that the solubility of the biurate is not increased by alkalies, for in all physiological conditions, and probably in all pathological ones also, with the exception of gout and rheumatism of some standing, we have to deal only with uric acid or a urate of which the solubilities are, as we know, very different from those of the biurate, and which do, comparatively easily, pass into solution in combination with an alkaline base, and are also precipitated from such solution by an acid which takes the base from them.

In so far as alkalies and their administration affect the solution and removal of biurate from the tissues, their first effect is, no doubt, to remove uric acid or urates and eliminate them from the body, and if this, as in the case of the salicylates above mentioned, causes subsaturation of the blood and tissue fluids, then some biurate is taken up from the deposits.

Hence the elimination of gouty deposits by the administration of alkalies is probably, as the late Sir W. Roberts points out (previous reference, p. 129), a somewhat slow process, though in taking his estimate of their effects we must make allowance for the constant daily introduction of uric acid or xanthins in food, which was probably, in the case he is speaking of, neither prevented nor allowed for; and when introduction is prevented, as I constantly aim at doing by diet, the subsaturation of the tissue fluids is increased and the resolution of biurate deposits accelerated.

Again, it is little to the point to show that salicylates have small effect on the solubility of the biurate, for both in physiology and pathology, when they cause a plus excretion of uric acid, they have to deal with a soluble urate; and if chemistry is correct they apparently have the power in conditions obtaining in the living human body of splitting this up into its constituents, and combining with only one of them, the glycocoll; and this power has, as I have pointed out in chapters ii. and iii., some relation to the salines in the blood and the acidity of the urine in relation to urea, and cannot therefore apparently be exercised in dogs.

Other things which interfere with the solubility of uric acid (such as iron, lead, mercury, lithia, zinc, manganese, calcium, &c.) may also produce an attack of gout, but compared to acids they are rarely met with in nature, and are not generally so powerful in action, because a good supply of alkaline phosphates or other alkaline salts easily prevents their producing much retention. Still at night,

when the acidity is high, they produce a little or increase any pain that is present.

Of iron salts Sir A. Garrod says (p. 383): "These preparations, when indiscriminately given to gouty subjects, are apt to excite paroxysms of their disorder, and are, for the most part, contra-indicated."

That lead precipitates gout attacks is so well known that I need hardly quote anything concerning it, but Sir A. Garrod has shown that gout is much more common among those exposed to lead, such as plumbers and painters. He also pointed out that uric acid is almost invariably present in the blood in cases of lead poisoning.

I would remark, in passing, that it is during the secondary action of lead that there is collæmia. Its primary action is (see fig. 13) to diminish the solubility of uric acid, to bring excretion below formation, and to retain it in the body, and at this time there is little in the blood. Then, when from dyspepsia or intestinal pain (due to urate of lead in the intestinal walls, see chapter x.) the urea and acidity fall, the retained uric acid is washed out into the blood stream, and collæmia with slow high tension pulse accompany and follow the lead colic. If my researches are correct, the slow high tension pulse which is often very marked in plumbism may be taken as proof positive of the presence of excess of uric acid in the blood, and the pulse can be quickened and its tension reduced by drugs that act on uric acid, and they may produce gout when so acting.

As to mercury, I have shown that its administration brings the excretion of uric acid below the level of formation (*British Medical Journal*, 1890, vol. i., p. 1241; also fig. 17) and clears the blood of it, producing mental well-being, free capillaries, quick low tension pulse and diuresis, all results of the free capillaries.

It also resembles lead in that it often produces some intestinal pain of a griping character.

Sir A. Garrod says of it (p. 236): "It is a well-established fact that metallic impregnation is capable of inducing pains in the extremities, which bear a close resemblance to those of rheumatism." Artificers exposed to mercurial vapour often suffer from what is termed "neuralgia mercurialis."

With regard to lithia, I must refer to what I have said of its action (fig. 14). My results show that it diminishes the excretion of uric acid, and at the same time frees the capillaries and quickens the pulse, causes mental well-being and a free flow of urine, and when it does all this it generally causes, like lead and mercury, some pricking and shooting pain in the joints also.

Now the mineral waters containing sulphates spoken of in the previous chapter as curing glycosuria and diabetes, and as doing this by clearing the blood of uric acid, are many of them, strange as it may seem, useful in the treatment of gout also.

They cure the diabetes by clearing the blood of uric acid and allowing combustion to improve, and we should expect that in doing this they would produce more or less arthritis, and this is exactly what we find to be the case; still, nevertheless, they do some good for gout, because once this first arthritis has passed over they tend to keep the blood free from excess of uric acid for some time, and in this way keep off attacks.

Unfortunately, the first arthritis does not always disappear and the blood is not always kept constantly clear of urate, but it fluctuates back and forwards; in this case a patient may come to the spa walking but leaves it on crutches. This result varies with the conditions present in each individual patient, with his strength, his nutrition, and above all with his digestion. If digestion is good the stimulation will succeed, the blood will be cleared of uric acid, and the smouldering arthritis will come to an end, as the joints are no longer bathed in uric acid. If, on the other hand, digestion is feeble, the blood will not be completely cleared of uric acid, there will be collæmia with fluctuations, and the arthritis will continue or increase.

It is by clearing the blood of uric acid that a large number of drugs (as iodides, salts of calcium, cannabis indica, lithia, guaiacum, other resins and compounds of sulphur, such as the troch. sulph. co. of Sir A. Garrod) act in relieving chronic arthritis associated with debility, and almost completely free from febrile temperature.

These troubles are due to the fact that there is chronic collæmia, and a very little rise of acidity, such as that which occurs every night, tends to drive almost every evening a little more urate into the joint, and keep the irritation smouldering on, but if any of the above-mentioned drugs can keep the blood relatively free from uric acid much of this chronic irritation may be prevented; but these drugs also when first used may make the pains worse for a day or two.

This is exactly the condition (chronic arthritis associated with debility) in which salicylates will do no good, and may even, as we shall see in the next chapter, do harm.

Exactly the same thing holds with regard to the mineral waters which contain sulphates; the patients arrive at the spa with a considerable quantity of uric acid in their blood, and the sulphates

drive this into their joints and produce an arthritis, and I believe that at several such spas the physicians are in the habit of telling their patients that this first attack is a sign that the water is going to do good.

And this is quite true, for once the first attack is over the sulphates keep the blood relatively clear of uric acid and thus prevent future attacks for some time.

And they produce these results (1) by clearing the blood of uric acid, and (2) by the increase of metabolism and combustion which results from this, and which, as we have seen, cures the diabetes, and the result of this upward metabolism is that the fires of life in this patient burn for a considerable time both brighter and better, acidity of urine remains high, alkalinity of blood low, and the blood is kept relatively clear of uric acid for some months, so that there is no arthritis. Indeed, it is obvious that so long as the blood contains no excess of uric acid an arthritic irritation cannot take up much urate from it.

But let the patient leave off the drug or the mineral water, and when, after a few months, his combustion has come down again he will again have collæmia, and each rise of acidity will then increase the irritation of his joints.

In this way the cure of the arthritis is not permanent, but has to be repeated from year to year; indeed, there is obviously no cure for these diseases but such alterations of diet as limit the introduction and formation of uric acid, and, at the same time, provide for its steady and continual elimination, thus gradually removing the quantities previously stored in the body.

Speaking generally, it may be said that all the diseases in the preceding fourteen chapters may be cured by such a drug as the iodide of mercury, which clears the blood of uric acid, but that this drug, or any other acting like it and removing the collæmia, may, in doing so, very probably produce arthritis (as we shall see in the cases recorded in the next chapter), but if it does not produce arthritis at once, then its continued administration will keep the blood clear of uric acid, and, for a time, prevent arthritis; such drugs can, in fact, produce arthritis only when they find a quantity of uric acid in the blood on which to act. On the other hand, it is nearly always possible to produce an arthritis by giving a solvent of uric acid, such as an alkali; thus, if some bicarbonate of soda is taken in the afternoon, this brings a little extra uric acid into the blood provided there is an available store, and when the ordinary evening rise of urinary acidity (or fall of blood alkalinity) supervenes

upon this, there is pricking and shooting in the joints; but this would not have occurred if the alkali had not been taken, because there would have been less uric acid in the blood—so little, in fact, that the rise of acidity would have produced no noticeable effect on the joints; and we have here, as it were, a summary of the whole action of uric acid in the causation of disease; and diet alone will cure or prevent the whole series of diseases, whether collæmic or retentive, because it diminishes the available uric acid.

In the same way a highly animal diet may, like the drugs and mineral waters mentioned above, not make a chronic arthritis worse, but better; for meat, and even uric acid itself, are stimulants to nutrition, because they clear the blood of uric acid and start an upward metabolism, and so long as the fires of life burn brightly the blood is kept clear of uric acid, and there is relative freedom from arthritis.

But a time comes in every case when this stimulation is no longer possible, when the fires of life, from age, over-work, and other causes of exhaustion, burn so low that they will not react to any stimulus, and then neither meat nor uric acid will do any more good; and then, instead of acting as a stimulant, the uric acid gets almost at once into the blood and causes depression of mind and metabolism.

So long as stimulation continues the patient is very pleased with the result: his arthritis is better, and he is better and stronger in himself; but he cannot leave off his stimulants; they have, on the contrary, to be steadily increased or all his troubles tend to return, and at the end he will have the most disastrous collæmia without any chance of escape from its results.

I believe that the treatment of chronic arthritis by a pure meat diet is a dangerous treatment, though in some cases, and where it acts as a stimulant, it does for a time relieve the arthritis; but where it fails to act as a stimulant, or after the stimulation passes off, it will produce serious results, and even in the last few years I have seen it apparently produce severe depression, headache, sleeplessness and anæmia (all the signs, in fact, of collæmia), and in one case even fits ending in prolonged coma. Then I notice that Dr. Armstrong, of Buxton, who read a paper at the Medical Society on this treatment in chronic gout (see *British Medical Journal*, May 1 and 15, 1897), gives as one of his conclusions in the original paper that patients "recover equally well whether on this (pure meat) dietary or on the meat-free dietary suggested by Dr. Alex. Haig"; if this is so, there is no shadow of doubt in my mind as to which

diet is the safer of the two, and after the above experiences no one for whom I am responsible shall be put on a pure meat diet.

In pathology we see that a gout attack is brought on by indulgence in wines and beers, which are more or less strongly acid. Champagne is about the most acid of wines, and the cheaper beers are generally more acid than those of better quality. I found acidity equivalent to 18 gr. of oxalic acid in a pint of 4d. ale, and 25 gr. in a pint of stout; sherry 37 gr. in a pint; port about the same; claret 46 gr. to the pint, and champagne 49 gr. to the pint.

Sir A. Garrod says (p. 226): "As regards acidity, Dr. Bence Jones has ascertained that wines may be arranged in the following order, beginning with the least acid:—sherry, port, champagne, claret, madeira, burgundy, Rhine wines, and moselle. All the wines are found to be more acid than malt liquors," but as the quantity of malt liquor taken is generally much greater than that of wine, the total amount of acid absorbed is greater in those who drink beer than in those who take wine.

Then the late Dr. G. Harley has pointed out the interesting fact (*Lancet*, 1896, vol. ii., p. 309) that the champagne used in England is often more acid than that in other countries.

A good class cider has an acidity equal to 58 gr. of oxalic acid to the pint, but it also contains a quantity of soda and potash, and the effect of taking it as regards the acidity of the twenty-four hours' urine is almost *nil*; I suppose, therefore, that its acidity is due to acid salts of vegetable acids which in the body are converted into carbonates, and as the acids and alkalies in cider or apple juice are nearly balanced, there is no effect on the acidity of the urine.

With wines and beers, however, this is not the case, for either by formation of acids during fermentation or by loss of alkali during fermentation and keeping (in the case of wine there is a deposit of acid tartrate of potash, tartar), the alkalies no longer balance the acids, and these beverages have a much more decided effect in raising the acidity of the urine than cider has; beer also is made from barley, in which acids preponderate over alkalies.

Fruits, again, are acid, owing to the acid salts they contain, but these become carbonates in the body, and act as doses of alkali rather than of acid, and they tend to lower the acidity of the twenty-four hours' urine.

I conclude that while many wines and beers have quite a distinct effect in raising the acidity of the urine, and will consequently cause retention of urates in the body and pave the way for gout, good cider made from pure fruit, unsophisticated, and apart from impurities such as lead, will do but little harm.

In reference to this I have been told by Dr. Bonus that a great friend of his, a native of Normandy, used to tell him that gout, gravel, and rheumatism were rare forms of disease there, and that this was attributed to the use of cider in place of wine: the same has sometimes been said of the cider-drinking counties of England, and I have known one or two people who asserted that their gout or rheumatism had left them on their giving up wine and taking to cider.

I have seen similar records with regard to gravel, so that I am inclined to think that cider or apples are good prescriptions in this trouble. Now, gravel is a collæmic disease, arthritis is a gout or precipitation disease; how is it, then, that one treatment will cure both? The gravel is a collæmic disease, and in accordance with the rule is relieved by a precipitant, therefore the cider acted as a precipitant; but how did a precipitant cure arthritis? The answer is that the arthritis spoken of was chronic, not acute, and that it was being kept up by collæmia, which allowed constant fresh uric acid to be brought to the filter; the cider relieved by putting a stop to this process, acting in just the same way as iodides, sulphur, guaiacum, and many sulphate waters, all of which are precipitants. Very chronic arthritis is thus under some conditions a collæmic disease, and is relieved by precipitants or by feeding up (see chapter xvi.).

Most fruits having a distinctly acid reaction tend to raise the acidity of the urine and diminish the alkalinity of the blood for an hour or two after they have been taken, and while they do this they often cause mental exaltation and well-being, with, perhaps, some pricking and shooting pains in the joints, or in a very gouty person an attack may be precipitated; but at the end of this time their alkaline bases come into action and there is a fall in the acidity of the urine and a rise in the alkalinity of the blood, which more than compensates for the previous fluctuation in the opposite direction, so that the effects of such fruits on the reaction of the urine of the twenty-four hours is to produce very little change.

Fruits, therefore, may be eaten when in season by those who have not much urate in their blood, and they will not cause much retention or accumulation of uric acid in the body.

I find it difficult to understand the logic of those who, wishing to know the effects of wines on the human body, have satisfied themselves by looking up the percentage composition of such wines in a work on chemistry, and then, finding that their order of acidity did not correspond with their apparent order of gout production,

have thence concluded that their acids or acid salts had no effect on the human body, and nothing whatever to do with the production of gout.

Surely if the object is really to find out the effect of wines on the reaction of the fluids of the body, it might be almost worth while to pour a known quantity of one or two of them into it and watch their effects on the reaction of the urine for instance; and this is an experiment which can be begun and completed in three to four hours of any single day.

The above view, that the acids of wine are not the cause of gout because their acidity does not correspond with their recorded production of gout, appears to me to quite lose sight of the obvious

FIG. 63.—CURVE OF URINARY ACIDITY SHOWING THE EFFECTS OF 2 OZ. OF SHERRY.

fact that the effect on the body depends not only on the acidity of the wine, but also on the quantity taken, so that beers of comparatively low acidity taken by the pint may nevertheless produce more effect than the more acid wines only taken by the ounce.

Now, fig. 63 shows the effect on the acidity of the urine of 2 oz. of sherry taken at 8 a.m.

The first point on the curve is the excretion of acid for the hour ending 8 a.m., the other points are the excretions of half-hours multiplied by two to make them comparable to the first point. The figures below are the hourly and half-hourly excretions of urine in cc. multiplied by the number of cc. of standard soda solution required to neutralise them.

The lower broken curve is that of a control day for comparison.

No food was taken for an hour after the sherry, by which time it had caused a very distinct rise in the acidity of the urine, a rise which is never seen in the normal curve of these hours (see fig. 3).

Note also that with the rising acidity the urinary water rose to 40 cc. in the half hour ending 9 a.m.; that it fell to 24 cc. at 9.30 and 10 a.m. is the generally constant result of the commencement of digestion, fluid being then required for gastric juice, as seen with every meal in fig. 3; the rise of acidity at 11 common to both curves is also a constant result of the later digestion of breakfast.

It seems clear that these 2 oz. of sherry produced a very distinct effect on the acidity of the urine.

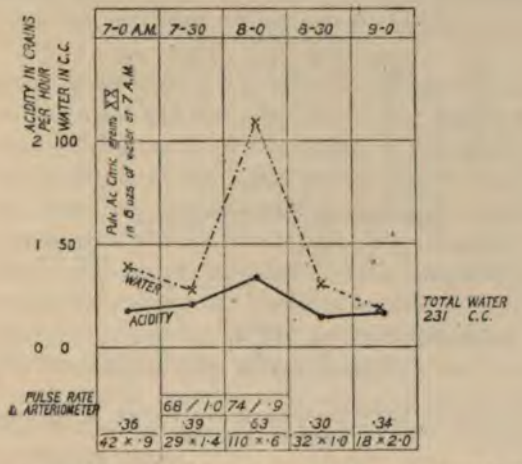

FIG. 64.—CURVE OF URINARY ACIDITY AND WATER SHOWING THE EFFECTS OF 20 GR. OF CITRIC ACID.

Fig. 64 shows a similar result from taking gr. xx. of citric acid in 6 oz. of water at 7 a.m. The upper curve is that of water in cc. per half hour, and the lower that of acidity of urine in grains per half hour, and as they are all for periods of half an hour none of them are multiplied by two.

The taking of the acid is followed by a rise of acidity to ·39 at 7.30, and to ·63 at 8, and a fall to ·3 at 8.30 a.m., when the ordinary curve appears to be resumed.

And now again note the urinary water (upper curve). It fell to 29 cc. in the first half hour, but rose to the great height of 110 cc. in the second half hour after the acid, this corresponding to the greatest rise in the acidity curve.

Note also the effects on the pulse rate and tension in the figures under 7.30 and 8 a.m. These read from left to right, 7.30 a.m., pulse rate 68, position sitting, diameter of left radial by arteriometer 1·0 mm.; and under 8 a.m., pulse rate 74, sitting, left radial diameter ·9 mm.

We see that along with the rise of acidity at 8 a.m. there was a quickening of the pulse, a fall of blood pressure allowing the diameter of the radial artery to diminish, and a diuresis; and these last were all results of one and the same cause, the relative clearing of the blood of uric acid which the fall of the blood's alkalinity produced.

We see also that the total urinary water in the two and a half hours ending 9 a.m. was 231 cc.

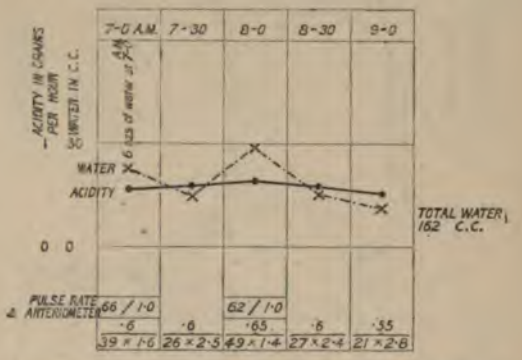

FIG. 65.—CURVE OF URINARY ACIDITY AND WATER, A CONTROL EXPERIMENT TO FIG. 64.

And now look at fig. 65, which is a control on another morning, when 6 oz. of pure water were taken at 7 a.m.

We see here that the acidity curve is nearly a straight line, that the water also fluctuates but little, its highest point being at 8 a.m., which is also the highest point of acidity; but there is no diuresis corresponding with that in fig. 55, though the same quantity of water was taken at the corresponding hour, and we see also why there was not, for the pulse remained slow and was indeed slower at 8 than 7, and there was no reduction in the diameter of the radial artery.

And we know why this was so, for there was no appreciable rise of acidity and no clearing of the blood from uric acid, and consequently the capillaries of the kidneys remained obstructed and the blood pressure did not fall.

Hence we see that the total water in the two and a half hours ending 9 a.m. on this day was only 162 cc., against 231 in fig. 64, thus again proving what I have been saying for years, that the uric acid controls the excretion of water, and that the water does not control the excretion of uric acid.

It is true that the water in the half hour ending 7 a.m. was 39 cc. in fig. 65, and 42 cc. in fig. 64, but that in the half hour ending 8 a.m. was only 49 cc. in fig. 65 against 110 cc. in fig. 64, and this accounted for most of the excess of the one total over the other, and it was clearly due to a freeing of the capillary circulation in the kidneys.

That the acidity curve as a whole is higher in fig. 65 than in fig. 64 is merely due to the fact that urea was higher on the one day than the other, as, other things equal, acidity rises and falls with urea.

These figures show clearly not only the effects of citric acid on the acidity of the urine and the alkalinity of the blood, but demonstrate once more that I can alter at pleasure the rate of the heart's action and the diameter of the radial artery, that is, the blood pressure, and can free from obstruction the capillary circulation not of the kidneys only, but also of the lungs, liver, muscles, skin, and indeed of the whole body; but that I have absolutely no power to do this except by altering the quantity of uric acid in the blood, of which the quantity passing in the urine is the index; and this again explains the fact that the excretion of uric acid and of water in the urine move from hour to hour and day to day in opposite directions, and everything that alters the uric acid may be depended upon to alter also the water.

I did not estimate the uric acid in fig. 64 at 8 a.m., but I am as certain that it fell as I am sure that I should have found increased excretion of water from the lungs as well as from the kidneys if I had looked for it.

It is not everyone who can give the time required to estimate the acidity of the urine or the diameter of the radial artery, still less the excretion of water from the lungs from half hour to half hour, but everyone can measure the urine half hour by half hour and note the alterations in the pulse rate and capillary reflux, and these would often give sufficient indication of the action of the drugs taken on uric acid; and when the doses taken and effects produced were larger than in these figures, distinct effects on the blood decimal could also be produced (see figs. 54 and 74).

They must not expect to produce the results shown in these

figures, except under the conditions which obtained in these experiments; that is, they must attempt to raise the acidity at a time such as the morning hours, when it is naturally steady or falling, and those again whose hourly excretion of acid is, from differences in diet, &c., greater than mine, must not expect to produce results comparable to mine except by using larger doses of acids.

Fig. 66 shows the similar results of taking 5 fl. oz. of stewed rhubarb and juice at 7 a.m.

Again we see a marked and decided rise in the acidity of the urine in the first hour after the dose, followed by an equally marked fall in the third half hour after it.

Here the pulse rate was counted, but no measurements of the radial artery were made, and we see that the pulse quickened from

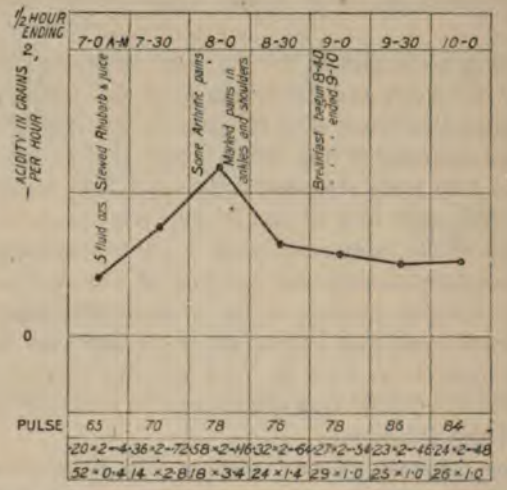

FIG. 66.—CURVE OF URINARY ACIDITY SHOWING THE EFFECTS OF STEWED RHUBARB.

65 up to 78 with the rising acidity, and fell to 76 as the acidity fell. That it rose again to 78, 86 and 84 at 9, 9.30 and 10 a.m. merely shows that the digestion of breakfast was then going on.

But part of the quickening of the pulse at 7.30 and 8 a.m. was no doubt due to the digestion of the rhubarb then going on in the stomach, and we see the same thing from the urinary water, which instead of rising with the rise of urinary acidity at 7.30 and 8, as in fig. 64, fell from 52 cc. at 7 a.m. to 14 and 18 cc., rose to 24 and 29 cc. at 8.30 and 9, and again fell to 25 and 26 cc. at 9.30 and 10, owing to the demand for water in the digestion of breakfast.

In fig. 64 there was practically nothing for the stomach to digest, and so the water was free to rise when the rising acidity cleared up the collæmia and freed the capillaries of the kidney. In fig. 66 these capillaries were no doubt also free at 8 a.m., but the blood was then poor in water owing to the pouring out of digestive fluids, and there was no diuresis.

This effect of digestion must be kept in mind in estimating the effect of drugs on collæmia and the renal capillaries as shown by diuresis.

The very marked arthritic pains about 8 a.m. (fig. 66) in the ankles and shoulders showed where the uric acid had gone, and no doubt if there had been any available water there would have been a diuresis.

A number of fruits containing acids or acid salts produce similar rises in the acidity of the urine for an hour or two after they are taken, with similar quickening of pulse rate and a relative diuresis, with mental brightness and well-being, and more or less arthritic pain; but very few of these in the quantities commonly taken produce any visible effect on the acidity of the twenty-four hours; the effect is no doubt there, but it is so slight as to be with difficulty distinguished from that due to other causes.

It is clear, then, that acid wines and fruits do affect the acidity of the urine, the alkalinity of the blood, and the solubility of uric acid.

In the case of fruits this effect is temporary, for later on their alkaline bases come into action and reverse the above effects; but in wines the alkali has either been removed from the grape juice or fresh acids have been formed or added; and beer has, for other though similar reasons, an excess of acid.

Before leaving the acidity of wines, however, we have to consider the effects of one of their other constituents, namely, alcohol.

Now Professor Vaughan Harley has pointed out that alcohol increases the excretion of uric acid, and it is scarcely likely that it does this in any way except, like very numerous other substances mentioned in this book, by affecting its solubility.

I have therefore taken alcohol in various forms, with a view of testing this effect, and my results show that it more or less distinctly diminishes the acidity of the urine, and, like other things which do this, increases for a time the excretion of uric acid.

In fig. 67 I show the effect of two small doses of brandy, the first at 11.30 a.m. and the second at 3.30 p.m., and in both cases its ingestion was followed by a distinct break in the upward curve of

acidity. In the half hour ending 11.30 before the brandy, the acidity rose from ·90 to 1·18 or ·28, but in the half hour ending 12 noon it only rose to 1·24 or ·06, and in the half hour ending 12.30 it rose again more quickly to 1·44 or a rise of ·20, and it seems therefore evident that the effect of the ½ oz. of brandy was to diminish the rise in the half hour ending 12 noon, just after it was taken.

Similarly in the half hour ending 3.30 p.m. the acidity rose from 1·57 to 1·66 or ·09, but in the half hour ending 4 p.m., after the brandy was taken, it did not rise at all; but it does rise again slightly in the half hour ending 4.30, making it probable that it would have risen at 4 p.m. also but for the brandy.

If the curve had risen steadily from 11.30 to 12.30 it should have stood at 1·31 at 12 noon, but it only reached 1·24, a loss of ·07;

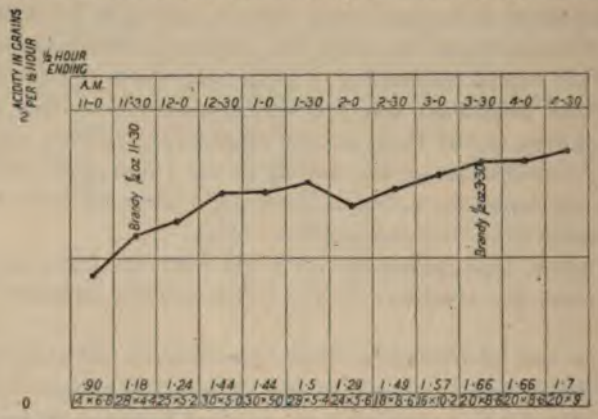

FIG. 67.—CURVE OF URINARY ACIDITY SHOWING THE EFFECT OF TAKING BRANDY UNDILUTED.

similarly the dose of brandy at 3.30 did away with a probable rise of about ·09.

I have several curves showing similar results from taking small doses of alcohol without water, and we shall not have much difficulty in understanding how they are produced. For alcohol and spirits generally act as irritants of mucous membranes, whether of mouth, throat or stomach, and this is especially the case when taken alone without added water.

Now if brandy irritates the mucous membrane of the stomach it may stop for a few moments the processes of digestion and absorption.

But the rise of acidity from 11 a.m. onwards is due to the digestion of breakfast and the absorption from the stomach of acids

and other products of digestion; just as the rise from 2 onwards is due to the similar digestion of lunch, therefore anything that interferes with digestion will interfere with the rise of acidity.

And we have tolerably clear evidence that alcohol does interfere with gastric digestion in the fact that in those not accustomed to it or who take it in unusually large doses, it may cause nausea and complete loss of the contents of the stomach by vomiting, or it may merely suspend digestion, the contents of the stomach being vomited more or less unchanged several hours later.

I think, therefore, that in the case of some wines rich in alcohol their effect on acidity would really be greater than that shown in the case of sherry (fig. 63) but for the alcohol they contain and its irritant action on the gastric mucous membrane. And we can now understand why Professor Harley found an increased excretion of uric acid.

It may also be interesting to remember here, as I have pointed out in chapter ii., that the mineral acids, if given in too large quantity, or insufficiently diluted, irritate and cause pain in the stomach, and then produce a fall in the acidity of the urine in place of a rise.

Before leaving the question of the effects of acids and acid salts on solubility and excretion, I will refer to a paper which Dr. Luff read before the Royal Medical and Chirurgical Society in June, 1898, and which is published in vol. lxxxi. of the *Transactions*, p. 375, on "The Influence on Gout of the Mineral Constituents of Various Vegetables."

In this he showed that he tried the ash of sixteen vegetables and found the order in which they affected the solubility of sodium biurate.

He then shows that this effect is not due to any single constituent of the vegetable ash, *e.g.*, the quantity of sodium, potassium or calcium salts, the phosphates, sulphates, or chlorides, and he leaves us in doubt on the point as to what the effect really is due to, and concludes by advising the use of spinach, which he places at the head of his solvent ashes, or of a salt which he prepares from this and other vegetable ashes.

But as I pointed out at the time this paper was read (see *Proceedings of the Royal Medical and Chirurgical Society*, Third Series, vol. x., p. 154), if Dr. Luff had carefully read my previous researches he need never have made these experiments at all, though I really am very glad that he did make them, as they confirm in a beautiful manner my results and those of Sir A. Garrod and others which preceded them.

And when we throw Dr. Luff's results into a table like that which follows, showing from his own figures the solvents (potash and soda) in each vegetable ash; and on the other hand the substances which had been shown by Sir A. Garrod and myself to hinder solubility, we at once see why the vegetable ashes produced exactly the effects Dr. Luff records.

It is a simple matter of balance, and the strongest wins: when the alkalies were in excess over calcium and acid radicals, solution predominated; when calcium and acid radicals were in excess over potash and soda, solution was much less. And this I point out is just what happens with all animal and vegetable mixtures, as the wines, beers, cider and other fluids we have just been discussing the resultant is the difference between the solvent forces and the retentive forces present in the given substance.

And when we apply this to Dr. Luff's results, order at once takes the place of chaos.

Order of Solvent Effect.	Potash and Soda.	Calcium.	Acid Radicals.
Spinach [1]	54·8	10·64	20·78
Brussels sprouts [2]	47·6	6·16	25·51
Cabbage [9]	40·1	17·14	28·36
Cauliflower [14]	34·2	23·33	41·13
Sea-kale [15]	36·4	27·56	43·24
Green peas [16]	44·6	4·98	42·08

In this table I give six out of Dr. Luff's sixteen vegetables; in the first column we have their names, and under each the number in brackets is the number of their place in his table of solution power of ash, that of spinach being most powerful, that of green peas least powerful.

In the second column is the total of potash and soda from Dr. Luff's figures. In the third column the total of calcium and in the fourth the total of acid radicals.

From this we can at once see why the ash of spinach stands at the head for its solvent effects; it has the largest amount of alkali, the smallest amount of acid radicals, and a moderate amount of calcium.

Green peas, at the other end of the scale, have less potash and soda than spinach, but more than double the amount of acid radicals. Peas also containing much more albumen than the other

vegetables, will cause a rise of acidity by the metabolism of their albumen.

The rest are more or less intermediate, thus cabbage has only slightly less alkali than green peas, but it has only two-thirds of its acid radicals, and a microscopic quantity of albumen.

It appears that the falling off in solvent power follows the increase of acid radicals more closely than that of the calcium, and this may be due to the fact that acid radicals are more soluble than the calcium salts.

But anyone can now see that the effect on solubility in glass, just as on the excretion of uric acid from the human body, is the resultant of the opposing forces.

It is quite useless, though it is an experiment which I have often made, to give mercury or a sulphate to retain uric acid with the one hand, while giving alkali or salicylate with the other; the victory or resultant rests with that which is present in largest force, or is favoured by external forces, *e.g.*, acids or alkalies in the food, or cold or heat in the surroundings.

It is also useless to give uric acid or xanthin in any form and expect a corresponding increase in excretion while administering mercury, iodides, sulphates, or other drugs that cause retention, or while there are powerful acids or acid-forming substances in the food, or even while the patient is exposed to cold.

The resulting excretion will be the resultant of these opposing forces, and the excretion of uric acid will only be proportional to the amount swallowed when its solubility in the blood is in no way interfered with.

Thus the things in an ordinary dinner might be arranged into those that hinder solubility and excretion and those that aid it somewhat as follows, and the result of a given meal will depend on the balance of forces.

	Hinder Excretion.	Aid Excretion.
Soup.	Xanthin and flesh salts.	
Fish	,, ,, ,, ...	Potatoes.
Meat.	,, ,, ,, ...	Spinach.
Pudding.	Sulphates and phosphates.	
Cheese.	Salts. Sulphur and phosphorus of albumens.	
Fruit.	Salts of acid reaction	Soda and potash.
Wine.	Acids and acid salts.	

It will be seen, then, that in such a meal the things that aid excretion are the potatoes and spinach and the alkali in the fruit, if

it is present, in a proportion nearly equal to the acid radicals, as in apples before mentioned.

The practical effect of most meals is a rise of acidity in the urine (see fig. 3), and this will be so in the above meal most certainly, unless the experimenter took very little soup, fish or meat, and no wine or acid fruit, and a large quantity of potatoes and spinach.

The excretion of uric acid after such a meal will, apart from the stores already in the body, depend partly on the amount taken in, in soup, fish and meat, and partly on the relative balance of alkalies over acid radicals.

The result in twenty-four hours will also depend upon whether the patient is warm in bed or the house the whole time, or is out and exposed to cold during an important part of the twenty-four hours, and this exposure to cold will have most effect when it occurs in the morning hours of the alkaline tide excretion, and we see the effects of this, for instance, in fig. 40.

And what applies to excretion applies also to the causation of gout or rheumatism, to arthritis, myalgia, lumbago, &c.; the result will depend partly on the amount of uric acid available and partly on the power or predominance of the forces that make for retention (acids, substances forming insoluble compounds, cold) over those that make for solution and excretion (alkalies, substances forming soluble compounds, warmth).

Thus, expose a man for two or three hours to a cold north-east wind at a temperature of 32° F., and he will come home with sufficient lumbago, sore throat, or tracheo-bronchitis, if he had excess of uric acid in his blood at the time of exposure; but he might be exposed to just the same temperature on another occasion, when from high acidity in the evening perhaps his blood was already almost clear of uric acid, without any ill-effects.

And those who are as far as possible free from uric acid, and pass out day by day in good solution all they form, will take practically no harm from exposure to cold at any time, although, as shown in the figure just mentioned, cold in the morning hours causes a quite visible fluctuation in my circulation curves and should therefore be avoided.

But if I were full of uric acid that fluctuation would be not merely interesting, but painful and dangerous.

It is clear, then, that Dr. Luff's treatment of gout by vegetables and vegetable salts is merely sweeping out with one hand the poison he introduces with the other, as he pays no attention to its introduction in flesh and tea, &c. And the vegetables have no occult

action in the matter, but simply that which is due to the preponderance of excretants or solvents over precipitants or retentives.

Sir A. Garrod says (p. 212): "That women are less subject to gout than men is beyond doubt." He attributes this to difference in character and habits, and adds: "Besides which, a most powerful counteracting influence exists in the presence of the catamenia during a considerable portion of their lives."

As to habits, women are generally less exposed to weather (cold and wet), and take less of beers and wines than men, and as to the catamenia I have shown (fig. 31) that menstruation lowers acidity and produces collæmia and a plus excretion of uric acid, and this occurring for four or five days in every month will sensibly diminish the amount of uric acid stored in the body.

In estimating the effects of beers, wines, and other beverages on different races, it is necessary to bear in mind the amount of meat or flesh food they consume, as this determines the introduction as well as the formation of uric acid, and obviously an acid will produce most effect and most quickly store sufficient uric acid to cause gout, where it has most to work upon and the formation and introduction are greatest. In England beers produce more gout than in Germany because the English consume more meat per head of population than any other nation in Europe (see *Lancet*, 1890, vol. ii., pp. 409, 468, and 589; and for similar facts about the incidence of gout in Persia see chapter xvii.).

Speaking of nationality reminds me of the fact that the Scotch suffer from gout comparatively little, so that our brethren north of the Tweed have difficulty in finding cases on which to work. I have no doubt that this is due to the fact that the national beverage of the Scotch, namely, whiskey, contains little or no acid, and affects acidity but little, and in fact, as we have seen above, aids excretion rather than retention. The Scotch also, as a rule, eat considerably less meat than the English. If a Scotchman comes to England and drinks beer and wine and eats meat, he suffers from gout like the Englishman. Sir A. Garrod says: "The least acid of all alcoholic fluids are geneva and whiskey."

It is generally agreed that excess of animal flesh is a cause of gout, and Sir A. Garrod quotes several authors to this effect, and he also says, on p. 230: "Cullen remarked that gout seldom attacked persons employed in constant bodily labour, or those who live much upon vegetable diet."

Figs. 46 and 47 demonstrate what would probably be the effects of constant bodily labour, and the evil effects of a flesh diet are evidenced by the figures from 24 to 28.

Dyspepsia may have an important influence, as I mentioned in speaking of Sir A. Garrod's quotations from Sydenham. It seems probable also, as pointed out by Bouchard, that acids may be formed under certain conditions or out of certain articles of food, and these would affect the solubility and excretion of uric acid so long as they continued to be formed.

It has been assumed by several writers, notably by Murchison, that in certain conditions of functional disturbance of the liver there is an excessive formation of uric acid. If they mean that uric acid is formed in greater proportion to urea than 1—35, I can see no evidence of it, and I look upon the excess of urates in the blood and urine as the sign of excessive excretion, a result of previous retention, and dependent upon the increased alkalinity of the blood which dyspepsia produces. If they mean that in certain liver troubles, especially those accompanied by slight fever, there is excessive formation of both uric acid and urea, in their normal relation to each other, I should raise no objection.

Among the symptoms of the dyspepsia connected with "the uric acid diathesis" mentioned by Sir A. Garrod (previous reference, p. 232) are many which I have attributed to collæmia, as "oppression and frequently sleepiness after food." "Saliva and buccal secretion often more adhesive than natural." I have pointed out that saliva is scanty in the collæmia of the opium rebound, and at the time of the uric acid headache, mental depression, &c., in all cases no doubt due to the same cause, namely, obstruction of capillaries by uric acid. "Accompanying these symptoms there is a scanty secretion of urine which is highly coloured and strongly acid." I have pointed out that the urine is scanty in the collæmia of the uric acid headache and mental depression, and that the water in fact varies inversely as the uric acid excreted along with it.

As to high acidity, that is only relative to the water. If the urine of twenty-four hours is saved it will be found that the total acidity is lower than that of the previous day, when there was less uric acid and more water, unless there is a great excess of uric acid in the urine, such as is met with in severe headache, epilepsy, paroxysmal hæmoglobinuria, and similar conditions, and then the quantity of uric acid present may itself suffice to raise the acidity of the urine decidedly.

Much sedentary work tends to produce gout. Sir A. Garrod quotes (p. 233) Sydenham as saying: "Whenever I returned to my studies gout returned to me," and I have already given his quotation from Cullen about the preventive power of bodily labour.

I have pointed out that the excretion of uric acid is greater in summer than in winter, and Sydenham speaks of gout as a winter disease. Now a labouring man has, so to speak, summer all the year round. His exertions keep his skin constantly active. He gets rid of a large amount of acid in this way, hence the acidity of his urine rules low, and the alkalinity of his blood is well maintained; he therefore excretes uric acid freely and retains little in his body, and so, as observed by Cullen, he but rarely suffers from gout, and this is so without much regard to his diet, for he excretes the uric acid he introduces, as well as that he forms. As to the acidity of the sweat, see also Heuss (*Monatschr. für Prakt. Dermatol.*, Band xiv., Nos. 9, 10, and 12, and *Lancet*, 1892, vol. ii., p. 1,118). A sedentary man has not only higher acidity and retention of uric acid, but his circulation, especially in peripheral parts like the hands and feet, is less well maintained, and as a result the alkalinity of the fibrous tissues in such parts is diminished.

Though I used to have headaches when my life was not sedentary, I have no doubt that I could indulge in meat and beer with comparative impunity if I lived the life of a labourer.

After what I have said about the effects of summer, it is not surprising to find Sir A. Garrod saying (p. 235): "Gout is undoubtedly much less prevalent in hot than in temperate climates," though, as he remarks further on, food and habits have also something to do with its absence.

The reverse effects of cold need hardly be gone into, but Sir A. Garrod says (p. 247): "When cold acts as an exciting cause the effect is due, at least in part, to its arresting the secretion of the skin and checking the escape of acid from the surface," and my experimental experience is in complete accord with this statement.

I notice with interest that Dr. Solly says (previous reference, p. 179): "The geographical distribution of gout is chiefly due to diet, drinking, and the social habits of the residents in countries where it is most prevalent, as in England for example"—a statement which I can most cordially agree with, for gout owes, not only its geographical distribution, but its entire existence, to diet.

Local injury will diminish the alkalinity of the affected part, just as fever diminishes the alkalinity of the whole body, and Sir A. Garrod says: "Local injury not only acts in exciting gout, but frequently determines the situation in which the inflammation will show itself. Thus, injury to the knee or ankle will usually cause these joints to be primarily affected, although the great toe or some other part may subsequently become implicated."

We shall see presently that in rheumatism local injury has the same effect, and compare the above quotation with what I have said as to the effects of exercise in determining the seat of the gouty arthritis.

Hæmorrhage is recorded by Sir A. Garrod as an exciting cause, and he attributes its effect to the "nervous depression" it produces. It seems to me, however, that another explanation is possible. First of all the blood is alkaline, and loss of blood is equivalent to removal of alkali from the body. Then when the temperature is normal severe loss of blood from any cause will raise it, and fever, as we have seen, raises the acidity. We have, therefore, two results of severe hæmorrhage, which diminish the alkalinity of the blood and tissue fluids. This interferes with the solubility of uric acid, and tends to precipitate it upon certain of the least alkaline tissues, namely, the fibrous tissues in the joints and elsewhere.

With regard to the raising of the acidity by fever, I am not sure that it should not be put the other way, and that it might not be more correct to say that rise of acidity or fall in the alkalinity of the blood causes fever. We have seen that acids stimulate nutrition, metabolism and combustion throughout the body, and cause a rise of urea and a rise of temperature if they produce a fall of uric acid; and if microbes and other materies morbi reduce the alkalinity of the blood they must of necessity cause an increase of metabolism and combustion, and this, as I have suggested, may be Nature's reaction, and an attempt on her part to burn up the invading microbe, in which endeavour we should, in my opinion, be ready to give her all the help in our power (see chapter ix.).

It is not a little interesting to find that acids stimulate both animal and vegetable nutrition, as, I believe, it has been shown that the growth of seeds and young plants can be greatly stimulated by watering them with dilute acids.

In any case the difference between the increased combustion we can produce with such drugs as the iodide of mercury, which quickens the pulse, raises the temperature, increases urea and diminishes albumin or sugar, and that of fever cannot be more than one of degree, and I have shown that in physiological conditions the quantity of uric acid in the blood controls to a very considerable extent both the formation and distribution of body heat (see fig. 5, also chapters viii. and xiii.).

That, as Sir A. Garrod relates, sudden stoppage of menstruation should produce gout is not extraordinary, for menstruation is commonly accompanied by collæmia and its signs (figs. 31 and 32),

and exposure to cold or febrile disturbance supervening upon this would, undoubtedly, drive the urate out of the blood into the joints, and it seems to me that in these cases the action of the nervous system, like that of Jupiter in ancient mythology, has been unnecessarily invoked from ignorance of the real cause.

One of the most interesting points about gout is the way in which it has been observed to alternate with troubles produced by collæmia, such as high blood pressure, headache, depression, &c., as mentioned in the chapters treating of these; and this is due to the fact that for some little time round each attack of gout the blood in general is kept relatively free of uric acid, so that severe collæmia is prevented.

Now there are two chief factors concerned in bringing about this result.

One is the fact that uric acid attracts uric acid; and everyone knows that if a few crystals of urate or uric acid are inadvertently left on a urine collecting glass they will increase very greatly from day to day, and every dirty urinal crusted with urates bears evidence to the same fact. The same thing occurs in the body, and the blood or tissue fluid passing over a deposit tends to give up its uric acid to the deposit (see chapter v.).

And there is probably another factor, as shown by Sir A. Garrod's observation ("Gout and Rheumatic Gout," Ed. iii., p. 110) that there is no uric acid in the serum drawn over an inflamed joint, which led him to suggest that inflammation destroys uric acid.

But the effect of the inflammation is to diminish the alkalinity of the blood and tissue fluids in the inflamed area, hence any blood that passes through this area will tend to leave its uric acid behind it in colloid form, because as we have seen in chapter v. slight acidification of a solution of uric acid in phosphate of soda tends to throw it down in colloid form, and the urate so retained eventually becomes a biurate, and is deposited in crystals.

But if the inflammation lasts only a short time it never becomes a biurate; but remaining in colloid form is redissolved, as the normal alkalinity is restored; and here we see the chief difference between the arthritis of rheumatism and that of gout, *i.e.*, between acute and temporary and chronic and persistent.

It is probably as the result of the action of these two factors that a patient who has for years suffered from headache, mental depression, or other signs of uric acid collæmia gets one day, as the result of some strain, blow, injury, or other local cause of alteration in alkalinity, an attack of gout in his toe; and then, perhaps, for several

years he has recurrent gout in this toe or other joints, and ceases to suffer from the signs of collæmia, but meanwhile he is accumulating a fine tophus in his foot, which acts as a uric acid filter for his blood and the rest of his body.

Later on some shock, illness, or severe injury depresses him, and then his blood becomes a better solvent of uric acid, and takes up from the tophus in place of adding to it; and so the gout in the toe ceases, and the collæmia, headache and depression return, together with an increased excretion of uric acid in the urine.

Later the sequence repeats itself and the collæmia is brought to an end by a fresh attack of gout, and this is the explanation of the well-known tendency of gout and rheumatism to recur and recur, often in the same fibrous tissue, once they have attacked it, whether this be part of a joint or of the mitral valve, of the pharynx, larynx, trachea, bronchi and fibrous tissues of the lungs, or of the cellular tissues in the stomach, intestines and pelvis; for there is left in such fibrous tissue either a condition of irritation and diminished alkalinity, or a few crystals of urate as mentioned in chapter ix., or both. And this accounts for the alternation between the symptoms of collæmia and those of arthritis, and the action of cold, acids and numerous metals and drugs in changing the former into the latter.

I notice with interest that Dr. Ewart * says on p. 310 that the assumption of the unknown factor "diathesis" is unnecessary, and on the next page he says that "marked uricacidæmia and demonstrable deposits of biurates are the features of declared gout."

On the other hand he declines to credit gout to mere excess of uric acid, because it (gout) is not a constant phenomenon of leucocythæmia, and does not very often occur in children, whose production of uric acid is so great.

If, however, rheumatism is due to urates, and is, as above hinted by several observers, but gout in a child, one of these objections at once falls to the ground; and leucocythæmia is a somewhat rare disease and occurs generally in conditions where there is great depression of nutrition and metabolism, and when consequently the condition of the blood and tissue fluids is, as regards acidity or alkalinity, at the very opposite pole to that at which gout occurs; but in the similar conditions of enlarged spleen with or after malaria, with the fluctuations in alkalinity of the fluids produced by recurring attacks of fever, gout is not at all uncommon, the leucocythæmia

* "Gout and Goutiness." By William Ewart, M.D.Cantab., F.R.C.P., London, 1896.

end of the cycle being represented, as in the case narrated in chapter ii., by attacks of gravel.

Later he quotes the views of others, which make a "depressed and faulty metabolism" the "first departure" and abnormal secretion its result; and makes the goutiness resulting from such faulty metabolism the basis of all articular gout.

My belief is, and it is steadily increasing and gaining strength, as I said at the Medical Society in November, 1896, with reference to headache, that "the uric acid diathesis" is a myth. If uric acid is controlled, that is, if there is neither excessive introduction nor excessive formation from excess of nitrogen, both gout and goutiness would gradually disappear or cease to be evolved, and this is a proposition which in one sense or other can be demonstrated.

I need not again go into my reasons for believing that depressed and faulty metabolism is a result of excess of uric acid and not its cause; but I can scarcely follow Dr. Ewart's reasoning in saying that the large excretion of uric acid which follows excess in nitrogeneous food is not derived from the food.

It will be seen from my facts and arguments as to hospital beef-tea, in chapter xvii., that a pound of meat from which it is made probably introduces the equivalent (in xanthins) of 7 gr. of uric acid, and if we credit a man who is taking excess of nitrogen with only ½ lb. of such meat a day, that would account for an introduction equivalent to 1,200 gr. of uric acid in a year, and if he also takes an absolute excess of nitrogen and forms, say, 100 gr. of urea per day more than he has any physiological right to do, he will also form nearly an extra 3 gr. a day of uric acid, or 1,100 gr. in a year.

It is clear, then, that if such introduction and formation do not account for any excess of uric acid met with in the urine after excess of nitrogenous food, especially in the form of animal flesh, it is not because they will not furnish the required quantity.

In this connection I will mention a case I have been told of by by friend Mr. Hope Lewis, of Auckland, New Zealand. It was that of an hotel-keeper who consulted him for bad temper, worst in the mornings, and general myalgia.

On inquiry, however, it came out that he was most moderate in meat and wine, lived carefully, and ate plenty of fruit, so that Mr. Lewis was at a loss to account for his condition, when the patient said: "I take several cups of beef-tea every day—really good stuff it is—my hotel is famous for it." And this is just my own experience, as I often see patients who take little or no meat; but then one is sure to find either that this is made up for in eggs

and fish, or that soup, beef-tea, or some of the urine-like fluids and extracts so largely advertised are being taken in its place. Indeed, one almost wonders that the manufacturers of these delicacies do not take a hint from the inhabitants of North Africa and South America, mentioned in chapter iii., and obtain a still larger supply of the same products by evaporating urine.

I may just mention here that a butcher at one time under my care with gout, Bright's disease and cardiac failure acknowledged to consuming 2 lb. of his own commodities per day; and it is little wonder that urates and their work were visible all over him, or that they had altered his joints and his blood, irritated his kidneys and dilated his heart, in the manner described in previous chapters.

It is interesting to note that these joint changes were marked, and would undoubtedly have been called rheumatoid arthritis if no urates had been visible.

His tissues are absolutely full of uric acid, and if I were now to put him on a uric-acid-free diet he would go on excreting excess of it for months and years, and during the whole time he would have the signs of collæmia, with the depressed nutrition and metabolism it produces.

And with the obstructed capillaries of the collæmia and his failing and dilating heart, he would have what we always find with these conditions, congestion of the liver (nutmeg) and of the circulation behind it; so that the poor liver again is blamed for the fault of others, and is not an original sinner.

In this way an accumulation of urates explains the continuance of collæmia for a long time after the diet has been altered. This is not "the uric acid diathesis" or faulty metabolism, but collæmia from previous urate accumulations. There was nothing wrong with this man's liver till he took to swallowing 14 gr. of uric acid a day in flesh. The arthritis, collæmia and congested liver were the results.

The kidneys, I believe, never refuse to pass uric acid unless they are inflamed, and then they have no choice, as the altered alkalinity of their tissues and fluids affects the solubility of uric acid.

What do we see in migraine while the kidneys are sound? A large excretion of uric acid, though urea may be diminished; but this is due to the fact that urea is diminished in the blood while uric acid is in excess in that fluid.

Similarly in the chronic stages and absolutely uninflammatory conditions of granular kidney we get, as I have often pointed out, a very large excretion of uric acid, so large that it may considerably raise the specific gravity of the urine and so upset the diagnosis of

granular kidney (see cases in chapter xvi.), or may cause more or less severe symptoms of gravel or calculus, and this because, for reasons already given in this chapter, the blood is full of uric acid.

The kidneys, just as the liver, muscles, skin, and all other tissues, are importantly affected by the uric acid, but they themselves always pass out uric acid when it is present in excess in the blood, except when, as in acute Bright's disease, they have their alkalinity diminished; but this is a chemical, not a physiological, refusal to pass it.

As to inherited gout, I would again ask how much of the inheritance is that of dollars and habits of feeding, and as in the cases of the children, with reference to whom Mr. Hutchinson is quoted at the beginning of the chapter: did they not live in their father's house, and did they not repeat his errors of feeding, both as to excessive introduction and excessive formation of uric acid (*i.e.*, excess of nitrogen above 9 gr. of albumin per lb.)?

To my mind, gout is poisoning by animal flesh, with tea and similar vegetable alkaloid-containing substances; and many theories have arisen from inability to understand the introduction, formation and solubilities of uric acid and their bearings on the results produced.

When the gout attack comes suddenly in the night and is in every way typical, there is not much to be said about the diagnosis, and salicylate of soda or aspirin in sufficient quantity will very quickly relieve it, as in my case in *St. Bartholomew's Hospital Reports*, previously mentioned. It is necessary, however, to give sufficient, and if gr. xx. can be given every two hours for acute rheumatism, I fail to see why it should not, if necessary, also be given for acute gout; certainly neither disease can be expected to yield to a dose of gr. x. three times a day.

I have seen salicylates fail to cure, but only under conditions where failure could have been foretold.

They are very little use by themselves in chronic rheumatism, and very little more in chronic gout without rise of temperature; again, where alkalies or colchicum have already been used, salicylates will not only be of no use, but may do harm, and again they are incompatible with the use of hot or Turkish baths, for reasons which will appear in the following chapter and in the descriptions of figs. 62 and 63.

Where alkalies, colchicum or hot baths have been used they had better be continued, unless all treatment can be left off for several days to allow intestinal digestion to recover from the colchicum, and the alkalinity of the blood to recover from the effects of alkalies and dyspepsia before the salicylates are given.

In very chronic gout their action may be improved by giving them with sp. am. aromat. or with iodides, or in alternate doses with acids or other substances which raise acidity. Of course care must be taken not to overpower salicylates with acids, but the acidity of the urine should be raised to normal. In these chronic cases salicylates may eventually do much good if steadily persevered with; either salicylic acid or its ammonium salt or aspirin will sometimes succeed where the sodium salt appears to fail. Salicylic acid with pulv. opii co. in a cachet is sometimes very useful in more chronic conditions. Again, where we have to deal with real uratic arthritis, the local application of salicylate of methyl should not be forgotten. This may be painted on night and morning and covered with gutta-percha tissue and a bandage. It may be used either alone or along with administration of salicylates by the mouth. In this case care must be taken not to give too much of the drug, as the methyl salicylate promptly gets into the blood and urine and produces constitutional symptoms, and if painted on too often or over too large a surface these may be severe, but for many local troubles it is the best way to use salicylates, and where salicylates by mouth upset the stomach it can replace them entirely.

In chronic conditions alkalies are decidedly useful, and the only rule I go by is to give them when the acidity of the urine is low and it does not appear likely that it can be raised. Then all acids must be cut out of the food and alkalies may be given to the extent of at least 80—100 gr. per day. By alkalies I mean the bicarbonates of potassium or sodium, chiefly the latter, and not on any account an ammonium salt, as this not only raises the acidity of the urine, but also forms an insoluble urate.

This applies to all conditions where solvents are required; in catarrh and bronchitis, as well as in gout and rheumatism, give plenty of alkali, and give it alone.

When giving alkalies you may cut down the quantity of food decidedly, as low urea and low acidity of urine help the alkali; but when giving salicylates, especially when there is little or no fever, you must feed up and even give acid fruits or wine, as fever, high acidity and acids help the action of salicylates. It is a very common mistake in the treatment of gout to cut down food when ordering salicylates, but this just ensures a condition in which they cannot possibly produce their best effects, and may do harm.

I notice with interest that in a discussion on the "Chemical Pathology of Gout" Professor C. von Noorden says (*British Medical Journal*, 1904, vol. ii., p. 740): "The rise of uric acid after inges-

tion of purin substances, appears in a gouty patient to be much more delayed than in the healthy." This is a very interesting observation, and its explanation is sufficiently simple. The gouty patient has deposits of uric acid scattered about in various parts of the body, which of course retain a very considerable quantity of the uric acid he ingests; and it is just here that we come in sight of the full importance of clearing out all the deposits that have taken place in the body, for, unless we do this, a part of each fresh dose of uric acid that is swallowed will be held back by uric acid filter action (see chapter v.), and thus the deposits in the body will increase instead of diminishing. Take a person who is not gouty, and who is practically free from deposits, either in the liver or the fibrous tissues, and the given dose of purin substances will be found in this case to pass into the urine almost grain for grain as swallowed.

It is at this point also that the greatest mistakes have been made in the past, *i.e.*, in judging of the effects of the administration of uric acid, and no one ever looked to see whether the uric acid administered got into the blood or remained there.

A little further on he is reported to say: "Alkalies in every form are utterly useless. They act excellently in nephro-lithiasis, but in true gout they cause diminution, that is, actual retention of uric acid."

I have often noticed this action of alkali, and before I made my uric acid filter investigations I was quite at a loss to explain it. Now, however, I know that it is a simple result of the uric acid filter action, and one which we have no difficulty in understanding if we bear in mind that urate irritation in fibrous tissues produces a local rise of acidity, and that such tissues are then the least alkaline places in the body.

When the dose of alkali is administered, its first effect is to sweep the uric acid out of the liver into the blood stream (and it does this for the simple reason that the liver is naturally the first place it gets to), but at this time there is not very much alkali in the general circulation, hence by uric acid filter action all that is swept out of the liver is caught up and retained in the various deposits in the tissues, which it serves to increase; and it is only later on, often much later, when a very considerable quantity of alkali has been taken, sufficient, in fact, to increase decidedly the alkalinity of all the tissues and fluids of the body, including the seats of uric acid irritation, that uric acid is at last taken up from all the deposits in the body and is then freely passed out of the body and through the kidneys; but so long as in any patient there is a single focus of urate

irritation which is less alkaline than the blood and tissue fluids generally, uric acid filter action tends to prevent it remaining in the blood and passing freely out of the body through the kidneys.

The reason that alkalies are thus useless in gout is because they are not given in sufficiently large quantity to increase the alkalinity of the tissues and fluids of the body, and this complete alkalinity may not occur until the urine has been steadily and constantly alkaline for several days. Thus one of the old original observations on acute rheumatism, which I have previously quoted, was that "the urine became alkaline and the pains were relieved." Until the urine did become alkaline, the retention of uric acid in the body by uric acid filter action could not possibly cease.

This is the reason alkalies often make chronic arthritis worse at first; they bring fresh uric acid into the blood, but are unable to prevent it from getting into the joints.

The cure of an arthritis or myalgia by alkali generally works out as follows:—

First day.—Alkali seems to have the effect of somewhat increasing the pain and stiffness; it brings an increase of uric acid into the blood, and some of this is attracted to the focus of trouble and increases it.

Second day.—Alkali getting more power; it begins to take up a little uric acid from the foci of trouble, hence pain and stiffness begin to diminish.

Third day.—Alkali now in full power; it takes up uric acid freely from all deposits and holds it all in solution; there is collæmic head or slight threatening of headache, and the arthritis and myalgia have vanished.

A precisely similar effect, the clearing of all uric acid out of places of deposit, is produced by a salicylate in from twenty-four to thirty-six hours; hence it cures more quickly than an alkali. Alkali, in insufficient dose, used to take six weeks to cure arthritis; salicylate now does it easily in three days.

In both cases the capillary reflux gives trustworthy information as to what is taking place; it slows when either solvent brings the extra uric acid into the blood, and in proportion to the quantity brought in. A reflux of 4 or 5 with the arthritis or myalgia will slow to 7 or 8 with the solution and collæmia which relieve them. I am here speaking of comparatively slight conditions and not of acute rheumatism, or the fluctuations would be larger.

With salicylates it is just the reverse, for though they of necessity come first to the liver and clear it out, still as soon as salicylate

is present in any quantity in the general circulation it clears out first the part which is least alkaline, and that is, we know, the joint where urates have been recently causing local irritation. Hence salicylates cure a local arthritis quickly in a few hours; alkalies take at least days to do it.

A little further on Professor von Noorden says (previous reference, p. 741): "With regard to treatment, we are all agreed that food containing an excess of purin bodies should be avoided, and those words embody almost all there is to be said as to dietetics." Here I am interested to see that my whole point is quietly admitted, for if all exogenous uric acid is excluded, so that the daily turnover of uric acid is reduced from something over 20 gr. a day down to 10 gr., then there is nothing more to be said, not only as to dietetics, but also as to etiology, pathology, and treatment, as this alone will demonstrate the whole three. It will show that the etiology is in the taking of poisonous and unnatural foods, that the pathology is concerned solely with the effects of the uric acid so introduced on the tissues and circulation, and that the treatment is concerned solely with the elimination of this uric acid.

If the principle of the exclusion of poisons is fully admitted, all the rest can be demonstrated, even, if need be, by those who have not studied physiology, and numbers of my patients soon learn to demonstrate for themselves the effects, both on the tissues and circulation, of the uric acid they swallow or refrain from swallowing; and, as seeing is believing, they very soon come to agree with me that when all exogenous uric acid has been excluded from our food we shall be a much more healthy and happy nation than at present.

I may mention here, as it bears specially on treatment, the well-known connection between gout and certain teeth troubles. And, indeed, it has been quite a common experience with me that the dental troubles called periostitis, or other inflammation of the pulp or surroundings of a tooth, such as are started by a cold wind in spring or autumn, yield at once and promptly disappear if salicylates are taken for any purpose.

It seems possible that we have here again to deal with a gout of fibrous tissues, originating, just like gout or rheumatism elsewhere, in the local action of cold, and like these yielding at once to the administration of salicylates.

I have gradually come to use salicylates with the utmost confidence in such troubles, and I have even found that their power is so great that the local application of a little salicylate of methyl to

the face over the painful tooth and its roots, night and morning or oftener, very promptly relieves and removes such irritation, so that in many cases there is no necessity to administer salicylates internally.

But drugs never go to the root of the matter, diet is the only thing that does; and though drugs may relieve for a time, I regard it as worse than useless to sweep out urates with salicylates and at the same time pour them in day after day in soup, fish, flesh, and tea. Here, as elsewhere, the results produced by diet can be estimated either from day to day or week to week with great precision from the changes in the capillary circulation, the granules in the blood, or the blood-decimal.

Gout is the great central type of the precipitation group, and practically the only things that have ever been found to relieve it have been solvents of uric acid, but better and more satisfactory than any such relief is the absolute and complete prevention of the trouble which a correct diet produces, and I will now mention shortly one or two of the very numerous records I get from gouty patients. One writes after two years on diet: "This was the first winter that I had passed during which I have had no cough or cold, and had been entirely free from rheumatic pains," and then the same patient, speaking of his general condition on diet, says: "I am as hard as nails." Then I have a large number of records from patients who have been on the uric-acid-free diet for from one to three years, and whose arthritis has more or less completely taken its departure as the result. Thus it is recorded: "Two years on your diet has cured the gout to which I was a martyr, and made me a new man"; and another: "Your diet has had a wonderful effect on her hands. The gouty swellings on fingers and thumb gone, and she can again play the piano like a young girl. Time on diet two and a half years." A general practitioner writes that he was a cripple, and retired from work with gout and pneumonia, but now, a year later, he is heavier, stronger and happier than for years. From many similar records I gather that the diet takes one and a half to two years, or in bad cases two and a half to three years, to cure arthritis, as I say in my diet notes.*

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*To be obtained from Messrs. John Bale, Sons & Danielsson, Ltd., 83-91, Great Titchfield Street, London, W. Price 12 for 6d., or 100 for 2s. 6d. net.

CHAPTER XVI.

Rheumatism and Morbus Cordis.

Much of what I have said about gout will apply also to rheumatism, and though they can often be clinically distinguished, I do not draw any hard and fast line between them, believing that the arthritis is in both cases due to the irritant action of uric acid on the fibrous structures of the joints.

An arthritis may or may not be due to uric acid, but it becomes certain that it is due to it if the patient is found to have less than the usual quantity of uric acid in the blood at the time of the attack, and if the arthritis is found to be relieved by solvents and increased by precipitants of uric acid; and when any arthritis, accompanied by fever, is not relieved by uric acid solvents, properly administered, the possible presence of septic arthritis, tubercle, or new growth should be considered.

I have suggested that salicylates cure acute rheumatism by effecting the elimination of urates, and I have shown that as regards the action of salicin, salol and a salicylate, the latter has most power, dose for dose, in eliminating uric acid, and has also most effect over the arthritis, while salicin has much less effect on uric acid and requires to be given in much larger doses, and salol is in both respects intermediate between the two (see *Medico-Chirurgical Transactions*, vol. lxxiii., p. 297).

I have further suggested that the action of uric acid as an irritant of fibrous tissues may quite as easily account for the endocarditis and pericarditis of acute rheumatism as for its arthritis (see *Practitioner* of February, March and April, 1891).

I have also remarked that while the chemistry and physics of uric acid are capable of completely accounting for all the phenomena of acute rheumatism, and the action of all drugs and diets that are useful in treatment, as much cannot be said for any other theory of its causation.

For instance, no satisfactory explanation of the value of alkalies among drugs, or of milk and farinaceous diet, or again of hot baths, blankets, and other sudorifics in general management, can be given on the theory that acute rheumatism is due to a miasm or microbe; while a comparatively rudimentary knowledge of the solubility of uric acid and the processes which promote its excretion and elimination suffice to explain them all.

In reference to these points I have formulated the statement: "All substances which promote the free excretion and elimination of uric acid do good in the arthritis which is due to it, and conversely all substances which hinder its excretion and elimination do harm" (*British Medical Journal*, 1888, vol. ii., p. 10). And though, as explained in the previous chapter, some substances which hinder excretion may yet, by keeping the blood clear of uric acid, prevent arthritis, it is quite true that these substances, when first given, are liable to produce an attack. Again, the pathological condition which most hinders the solubility and excretion of urates (namely, fever), has just the same effect as the drugs which do this, and frequently precipitates an attack of general uratic arthritis; hence we are told by a writer in the *Lancet*, 1893, vol. i., p. 918, that "enteric fever at its very commencement may present the picture of acute rheumatism." I believe that any acute fever may present this same picture, provided there was in the blood, at the time the temperature began to rise, sufficient uric acid to irritate the joints when it was concentrated upon them, for fever diminishes the alkalinity of the blood and diminishes its powers of holding urates in solution; and I have already pointed out in chapter xv. that the blood is in this way most completely cleared of urates at the beginning of the fever, which corresponds exactly with the observation of the writer quoted above. And I have myself seen several cases in which the onset of enteric fever has been mistaken for acute rheumatism.

The theory that acute rheumatism is an infective disease and due to a micro-organism which causes the production of lactic acid, has been prominently brought forward by Dr. Newsholme in the Milroy Lectures (*Lancet*, 1895, vol. i., p. 589), who points out that there have been epidemics of rheumatic fever in certain years, and that rheumatic fever is an urban disease more than a rural.

I have always acknowledged that rheumatic fever may be precipitated by any fever, however caused, whether by a specific micro-organism as in the above cases of enteric, or by acute dyspepsia as commonly seen in a schoolboy from (?) natural causes. Anything that diminishes the alkalinity of the blood, and all fevers do this,

may produce rheumatic fever if there is plenty of uric acid in the blood at the time.

Now we are liable at many seasons to epidemics of catarrh, influenza and tonsillitis, not to mention cases of ill-developed specific fevers such as measles, scarlet fever, &c., which are overlooked and pass unrecorded, and any of these may produce corresponding epidemics of rheumatic fever; but there is here not the smallest proof that the rheumatic fever is due to the specific micro-organism and not to the effect of the fever on the alkalinity of the blood.

And Dr. Newsholme himself tells us that other specific febrile diseases, as enteric, scarlet fever and erysipelas, are affected in the same way as rheumatic fever, by season, rainfall, &c.

Exactly so; the epidemic of rheumatic fever varies with the epidemic of these diseases because the rheumatism is sometimes the result of these diseases.

Then as to rheumatic fever being an urban disease rather than a rural, this may show merely the relation of acute rheumatism to increased meat eating, which is more common in urban districts, and gout is, doubtless for the same reason, an urban rather than a rural disease; but I have never heard this used as an argument for its being infective.

Dr. Newsholme looks upon throat symptoms as a part of the disease, and the place where no doubt the micro-organism obtains an entrance into the body; but if this is so how does an alveolar abscess serve to precipitate a relapse? or how does an injury to an ankle or shoulder, when the skin is unbroken and no micro-organisms are introduced, serve to bring on acute rheumatism?

In a word, every micro-organism, specific or other, that produces fever may produce rheumatism, and then there are several other things, not in any way connected with micro-organisms, which will do the same; but all these things—injuries, micro-organisms and drugs—affect in one and the same way the solubility of uric acid in the blood, *i.e.*, they render it insoluble in that fluid.

Dr. Newsholme points out that the tendency to relapse is common to rheumatism and other fevers; but he is also kind enough to allow that frequent relapses occur when animal food is given too early after an attack.

This parallel is little more than skin deep on the surface of the word relapse, for surely a relapse after enteric fever is one thing and a relapse after rheumatic fever another and a totally different thing.

It is possible to prevent the relapse of acute rheumatism by con-

tinuing the salicylates or by abstaining from giving the animal food or the iron; but is it possible to prevent the relapse of enteric fever?

Again, the relapse of acute rheumatism can be produced—is, in fact, generally produced—by some error in treatment. I have seen many such relapses, and know exactly how they were produced, and so would anyone else who understood the solubility of uric acid and watched the treatment carefully; and I will undertake to produce relapses in any patient who will consent to its being done.

Again, if acute rheumatism is due to a micro-organism, how is it that salicylates cure it in proportion to their power of eliminating uric acid? I can now also show (see cases narrated further on) that if anything prevents their acting as solvents of uric acid they fail to cure it.

From the other side it would have to be shown that salicylates prevent the growth of the micro-organism; and that iron, lead, mercury, and other metals increase its growth as they make the pains worse.

The finding of a few micro-organisms in the fluids of a case of acute rheumatism is to my mind a very long way from affording proof that the acute rheumatism is due to the parasites, except quite indirectly.

I should admit that it might be due to them if they altered the alkalinity of the blood or produced fever; but, nevertheless, in a person who was free from excess of urates in the blood they would have no power to produce either arthritis or other irritation of fibrous tissues, and, as I have pointed out in previous chapters, many parasites seem to be unable even to produce fever in those whose blood is free from collæmia; and in illustration of this we find that those who suffer from arthritis with the onset of enteric fever are patients who have previously had arthritis or have marked signs of the presence of collæmia at the time of onset of the fever.

Again, to have an attack of a microbic disease often protects the individual affected from further attacks; but in rheumatism this is not the case, for the patient who has had one attack is more liable to have another; and this is also a marked characteristic of gout, for which a microbe has not, I think, as yet been suggested. In the case of gout we have a quite satisfactory physical explanation which we have discussed at length in connection with the phenomena of the uric acid filter, and I see no reason why the same explanation should not apply to the arthritis called rheumatism; indeed, my practical experience convinces me that it does so.

I shall now examine the points of difference between rheumatism

and gout, and see how far the different conditions under which the uric acid acts at different periods of life will enable us to explain them.

My friend, Dr. A. E. Garrod, mentions my researches on uric acid in the most kindly manner ("A Treatise on Rheumatism," p. 27), but yet objects strongly to my suggestion that acute rheumatism may be due to uric acid. He says: "Many objections present themselves to such a theory of acute rheumatism, which appears to me to attach undue importance to the articular troubles, whilst offering no explanation of the occurrence of the cardiac and other visceral lesions of rheumatism." I believe, as I have said (*Practitioner*, February, 1891, *et seq.*), that uric acid is quite capable of producing all these lesions, and I shall go into the matter presently; and Dr. Garrod goes on: "Again we have the fact that uric acid has not been found in the blood of rheumatic patients, which Dr. Haig explains by supposing that this substance is driven out of the blood into the joints by the high and rising acidity due to the fever; but no deposit of sodium urate is found in the joints. Lastly, it is difficult to believe that the same *materies morbi* is capable of giving rise to two such different disorders as rheumatism and gout."

This last statement is somewhat indefinite, but I hope to show that the differences are those of degree rather than of kind, and that they are due to differences in metabolic activity, functional activity, or chemical condition, which affect differently the solubility of uric acid, while the total quantity present also differs in the two conditions.

It has never been a matter of surprise to me that Sir A. Garrod was unable to find uric acid in the blood in acute rheumatism; on the contrary, if he had found a large quantity in the blood, it would have been a death-blow to my theory of its causation.

He does find it in the blood in gout because gout is a local disease, in which the acidity of one or two joints is specially raised, and in these all the uric acid that the blood brings in their direction is rendered insoluble and retained, giving rise to irritation and inflammation; but there is no general and complete clearing of the blood from uric acid, except in so far as the specially affected joints take it up.

In acute rheumatism the conditions are different; there is a general rise of acidity which clears all the uric acid out of the blood, driving it into the joints and elsewhere; little or none remains in the blood because the alkalinity of the whole circulating fluid is diminished; while in gout, though alkalinity generally is diminished,

it is only in the especially affected joints that the urate is rendered completely insoluble.

This explains a fact previously mentioned, that when I intentionally produce an arthritis by giving acids the clinical picture resembles rheumatism rather than gout, because I diminish the alkalinity generally, and drive the uric acid out of the blood into joints and fibrous tissues generally; if I want to imitate gout I must diminish the alkalinity generally to some extent; but I must also produce local irritation and rise of acidity in a joint by a blow, seton, or other injury, and this will precipitate the uric acid locally, while the blood still contains some.

In further objection to my explanation Dr. Garrod goes on to say, "but no deposit of sodium urate is found in the joints." He evidently considers the fact that the urate is not found there after death as equivalent to proof that it has never been there.

My researches have led me to take a different view and to believe that even in gout, when urate is retained, so to speak, in mass, and eventally thrown down in crystals of biurate, it may be removed so completely as to leave little or no trace of its presence after death, except the erosions in cartilage, &c., which some weeks, months, or years before death were completely filled up by it.

Much more so in acute rheumatism, where the urates are not present in mass, are only present for a few hours and in the form probably of colloid urate, and produce merely a little interstitial irritation. So soon as the acidity which drove them into the joints falls away, and the alkalinity of the blood rises, the urates in the joints are quickly taken up in solution in the blood, and passing through it arrive at the kidney and are excreted. Hence the excretion of uric acid is directly as the alkalinity of the blood, and inversely as the acidity of the urine, a relation which holds both in disease and in health, and can be demonstrated artificially at any time by using drugs which affect the alkalinity. As previously pointed out, Sir A. Garrod suggested that uric acid, when in the blood, is attracted differently by different organs, and that in certain organs, which for various causes are less alkaline than the blood, "the uric acid becomes less soluble and more easily retained" ("Lumleian Lectures," *British Medical Journal*, 1883, vol. i., p. 549).

If this be granted, and if, as is also shown by Sir A. Garrod, the cartilages and fibrous tissues of joints are both less vascular and less alkaline than the other tissues or the blood (see previous chapter), then the arthritis produced by uric acid is a simple matter of solubility, and can be produced at pleasure to almost any extent, and this I believe to be the case.

But there are other fibrous tissues in the body besides those of the joints, and what is to prevent them from being occasionally less alkaline and from suffering in consequence from a precipitation of colloid urate upon them and the irritation it sets up?

What about the fibrous tissues in the great lumbar fascia (lumbago), of those that form the sheaths of great nerve trunks (sciatica), and of those again that support the various coats of the intestinal walls (colic), of which I have already spoken, or of the fibrous tissues in the pelvic organs and fascia, especially in women, not a few of whose pains and inflammations may have an identical pathology with that of gout of the intestines (chapter x.)? And that some of these inflammations in women are rheumatic has already been suggested by Dr. Gervis.

But there are fibrous tissues in a more vital organ than any of these, an organ which is sometimes said to be in part analogous to a joint, and is often affected along with the joints in acute rheumatism. I mean the heart.

Will anyone who has looked at a transverse section of the heart wall tell me that the visceral layer of the pericardium is not continuous with fibrous tissue, which fibrous tissue forms the fascia of the heart muscle, and that the fibrous tissue of the endocardium on the opposite side of the wall is not also continuous with the fascia of the muscle in the same way?

Now muscles become acid as the result of contraction (Foster, "Physiology," 1877, p. 49), and if in some regions of the cardiac muscle, in proximity to its fibrous investment, the products of functional activity and contraction are not quickly removed, the muscle and its adjacent fascia may have their alkalinity so far reduced as to form foci, in which the uric acid circulating in the blood becomes, according to our premisses, "less soluble and more easily retained."

Such retention, also in accord with our premisses, giving rise to local irritation, which further reduces the local alkalinity, more uric acid is deposited, and so on till a considerable area of inflammation going on to proliferation of fibrous tissue and scar formation results.

If this may be the effect in the lumbar fascia, why not also in the pericardium and endocardium? The same causes that drive uric acid into the joints and set up arthritis may drive it into the fibrous tissues of the heart and produce endo- and pericarditis.

Then with reference to microbic origin, it has been pointed out (*British Medical Journal*, 1900, vol. ii., Epitome, p. 64) that the pericarditis of Bright's disease, when the blood, we may remember, is full of granules, is aseptic and sterile.

A somewhat new light is, I think, thrown on the effects of pericarditis on the function of the heart by the ingenious suggestion of my colleague, Mr. H. L. Barnard (*Lancet*, 1899, vol. i., p. 1080), that the pericardium bears to the heart muscle the same relation that the leather case of a football does to its expansile inner casing, or that the outer case of a bicycle tyre does to its inner case; in a word, that the heart is protected from sudden and disastrous dilatation by the strong fibrous pericardium, its outer casing.

It follows that if there is general inflammation of the pericardium, its strong resisting support may be replaced by bulging and yielding in various directions, and thus severe dilatation of the heart may quickly supervene.

We can now see the importance of absolute and complete rest in all such cases, and the value of the method mentioned on a future page of giving iodides with salicylates to keep down the blood pressure till the inflammation of the pericardium subsides and it has time to consolidate and get strong once more.

For Mr. Barnard's very interesting remarks on the rush of blood into the heart, which muscular contraction, especially the action of the abdominal muscles, can produce, and the value of the pericardium in resisting undue distension of the heart by such forces, I would refer to his paper.

With the useful instrument which Mr. Barnard and Dr. L. Hill have invented (see chapters v. and xviii.) we can gauge very accurately from day to day what the systemic blood pressure is doing, and what power it may have of dilating the heart and pericardium.

Mr. Barnard also points out that once serious softening and dilitation have taken place, the pericardium, like the outer casing of a tyre, may be beyond repair.

But here, I think, the parallel does not hold entirely, for the pericardium is not made of lifeless fibre and rubber, but of living tissue, which, given time and freedom from pressure, will certainly consolidate and contract, and become perhaps even stronger than before; but then, unfortunately, its undue thickening and contraction may become a danger to the nutrition of the heart muscle within it.

These facts, and my own experience of cases, leave in my mind no doubt that the two great causes of dilatation in rheumatism are (1) the softening of the fibrous pericardium, or similar injury of the cardiac muscle which rheumatic inflammation produces, and (2) the high blood pressure due to excess of uric acid in the blood. And in rheumatism the one condition is constantly alternating with the

other. No sooner has uric acid strained the heart valves and pericardium and then been precipitated on those fibrous structures causing inflammation and softening, than the debility which supervenes brings it again in excess into the blood (collæmia), and this dilates the heart and strains still more the damaged valves and pericardium.

A rational understanding of this causation and a rational treatment of uric acid and collæmic high blood pressure, the extent of which we can now measure in capillaries and larger vessels with accuracy, are the most important points. The value of iodides and salicylates in treatment is due to their affecting both the causes mentioned above. The salicylate removes uric acid from the damaged fibrous tissues and lessens their inflammation, while the iodide prevents the excess of uric acid, which the salicylate brings into the blood, from combining with alkali and producing severe collæmia, which would increase the strain on the damaged valves or pericardium.

We know (chapter iii.) that the effect of salicylates in rheumatism is to slow considerably the capillary reflux, as they increase the granules in the blood.

The effect of an iodide, on the other hand, is to diminish the granules in the blood and quicken the capillary reflux, and we must take the capillary reflux and the blood pressure as our guides and use the one drug to neutralise the evil effects of the other.

But as regards the endocardium, this is by no means the whole story, as there are causes just such as those which are active in the case of the joints, namely, friction and percussion, which may affect its alkalinity also. And we can now see that the pericardium is subjected to pressure and strain by any force that tends to dilate the heart.

Just as in the case of the joints, the heat and friction of exercise determine which joints shall be least alkaline, and so get the largest share of the uric acid; so in the heart the fibrous tissues of the valves suffer from friction and percussion, and are rendered the least alkaline of all the fibrous tissues of the heart at a time when there is a general fall of alkalinity.

Now, the effects of exercise on the reaction of the valves of the heart will be greatest where the work and strain are most severe, this accounting for the incidence of the chief rheumatic changes in the left side during extra-uterine and the right side during fœtal life.

In this way any unwonted exertion or strain on the heart, by giving rise to a little local irritation on the opposing surfaces of the

mitral or aortic valves, may diminish the local alkalinity, cause a local precipitation of uric acid and consequent irritation, and this irritation may be repeated and repeated till what were at first scarcely visible pin-point nodules of irritated connective tissue come at last to form well-marked nodules and scars.

Such a process of reasoning helps us to understand how a small local irritation in the mitral valve is carried on and on by a frequently recurring uric acid irritation till the whole valve is reduced to the condition of a thickened scar, and we have to deal with the final stages of mitral constriction.

And as an excess of uric acid in the blood obstructs all the capillaries and raises blood pressure (chapter v.), it is clear that it must throw increased work on the left side of the heart, first of all on the aortic valves and then, during systole, owing to the increased resistance to be overcome, on the mitral valves also; and anyone who has listened to the loud banging of the aortic valves during a uric acid storm (in migraine, for instance) will have no difficulty in realising what I mean.

Thus the valves of the left side of the heart are most exposed to injury by friction and percussion at the very time when there is an excess of the irritant uric acid in the blood ready to be precipitated upon them should the heat of action cause them to lose for a time their normal alkalinity.

And once a spot has become invaded by uric acid the irritation is always liable to be kept up and repeated until a serious and extensive lesion has been produced.

We have, then, certain conditions to which fibrous tissues of the heart are liable in common with all the fibrous tissues of the body, tending to precipitate uric acid upon them, and we have certain other conditions which are common to the fibrous tissues of the heart valves and those of the joints. Can we wonder that these structures are so often affected at the same time? and doubtless the liability of the endocardium to friction, percussion and strain accounts for the greater frequency of endocarditis as compared with pericarditis.

With regard to the causes that determine the structures that will be invaded by uric acid, I will quote what Dr. Garrod (*loc. cit.*, p. 82) says as to the order of invasion of joints: "The influence of external causes in determining the seats of the lesions is far less conspicuous in rheumatism than in gout, but as has been already stated, when rheumatic fever follows an injury the joint nearest to the seat of injury is usually the first to suffer."

Exactly so! The injury diminishes first of all the alkalinity of the affected structures, and then, if it is sufficiently severe to cause general fever, the alkalinity of the whole body is diminished. The uric acid is first rendered insoluble near the injured structures (hence these are the first to suffer), and later on in other fibrous tissues of the body (see Uric Acid Filter experiments, chapter v.).

Dr. Garrod also says (same page): "Dr. Fuller has laid special stress upon the liability of joints which have been the seats of local mischief. Dr. Maclagan also regards strain as the most important influence at work in determining the seat of rheumatic lesions, and Dr. Peter Simpson and others have expressed their belief that the joints which are most exercised are specially liable to rheumatism. M. Besnier, who is inclined on the whole to agree with them in this opinion, does not think that the rule is sufficiently general for the establishment of a definite law."

There is no necessity to establish a definite law, but every one of the conditions here mentioned can be quite easily translated in terms of uric acid causation.

Joints that have been the seat of local mischief will contain a certain amount of fibrous scar tissue, which, as we know, is lowly vascular, and this will easily have its alkalinity reduced and very slowly recover it again, and meanwhile uric acid will be accumulated and retained in it.

And the same argument will apply whether the local mischief was in the first instance due to uric acid or to external agencies. Once a scar has been produced, uric acid will account for its continued irritation and progressive enlargement.

Thus, suppose a young woman has acute rheumatism, and a few pin-point nodules are left on the mitral valves; she apparently recovers from her attack, and perhaps no murmur has been heard, but the valve, nevertheless, has been damaged to the extent of the above nodules, and these form microscopic scars, on which, however, uric acid will be again precipitated at the first opportunity.

And it may not have very long to wait, for every woman has more or less collæmia at her menstrual period (fig. 31); and this, by the increased blood pressure it produces, may strain the mitral valve, diminish the alkalinity of the damaged nodules, and then, as the alkalinity is generally diminished at the end of menstruation, clearing the blood of uric acid and putting an end to the collæmia, some of the urate in circulation may be precipitated upon the mitral valve, especially upon its damaged portions, and increase of lesion results.

And when this process is repeated month after month for years, we can easily understand how a microscopic scar becomes at last a leathery and calcareous mass, and why a buttonhole mitral is more commonly met with in women than in men.

We can also understand the connection which some have noticed between dysmenorrhœa and certain rheumatoid joint changes, for dysmenorrhœa means a more than usually marked fall of urea and acidity, a more than usually severe collæmia, and consequently more severe and widespread irritation in the already damaged tissues of joints or valves.

So that these changes in fibrous tissues due to the irritation of uric acid are more liable to progress from small to great in women than in men, and are still more liable to do so in those women who suffer from dysmenorrhœa, and again this dysmenorrhœa is often a result of congestion due to collæmia, and when we understand this causation we cease to wonder that correct diet so often makes a clean sweep of these troubles.

Before leaving this subject I must quote what Dr. Garrod says (*loc. cit.*, p. 53) on the influence of sex: "Dr. Cheadle has called attention to the greater liability of girls to almost all the individual manifestations of the disease, and my own observations lead me to think with him, that not only chorea but also subcutaneous nodules, erythema, and rheumatic heart affections are considerably commoner in female than in male children. It should be mentioned, however, that Hirsch found that rheumatic fever occurred more commonly in boys than in girls under the age of fifteen." From this latter statement we may, perhaps, infer that it is more common in girls after fifteen, when the menstrual influences I have spoken of come into play, and when at this time of life girls dash at one bound from childhood into womanhood. These factors must affect the formation and excretion of urates and increase for a time the possibilities of acute rheumatism, of collæmia and its results; and Dr. Cheadle says (*Lancet*, 1889, vol. i., pp. 824, 871) that girls of 10 to 15 years old are twice as liable to rheumatic fever as boys of the same age (see also fig. 59).

I agree with the authors quoted by Dr. Garrod that the joints which are most exercised are specially liable, and believe that it is often possible to tell the occupation of the patients by observing the joints chiefly affected.

With regard to this, I am indebted to Dr. Aylmer Dumat, of Durban, for the interesting observation that precisely the same relation to exercise holds for the severe myalgic pains which accompany the onset of dengue, and he narrates how both in himself and

in patients, an attack coming soon after a long or hard ride was accompanied by pains which were most severe in the adductor muscles of the thighs. He also gives it as his opinion that the feeling of intense fatigue which precedes the myalgic pain is due to uricacidæmia. It almost seems as if dengue furnishes but one more instance of the power of a febrile epidemic disease, perhaps akin to malaria, or still more to influenza, to produce rheumatism just as is done by the febrile diseases discussed in reference to Dr. Newsholme's theory on a previous page.

The pains of rheumatism resemble, I believe, those of gout in being worse at night and better in the morning; that is to say, they correspond with the natural fluctuations in the uric acid excretion, though this may be less conspicuous in rheumatism than in gout, as the former, being an acute disease, overpowers for a time the natural fluctuations; and in accordance with this the first symptoms may occur at very various hours.

The causes which precipitate the attack are just those which would be certain to raise the acidity of the urine and diminish the alkalinity of the blood—*e.g.*, a chill, getting wet through, or sleeping in a damp bed; the excretion of acid from the skin is interfered with, up goes the acidity, a certain amount of uric acid is driven into the joints, this causes some fever, and the rise of temperature still further diminishes alkalinity and sends all the uric acid into the joints.

Temperature in rheumatism at times resembles that of gout in being high at night and lower in the morning; at other times the highest point is in the morning. Of the temperature curves given by Dr. Garrod (*loc. cit.*, p. 60) of rheumatic fever treated upon the expectant plan, in fig. 1 the highest points are in the evening, in fig. 2 they are for the most part in the morning, and in fig. 5 there are some in the morning and some in the evening, though the morning preponderates.

I think that this is not difficult to explain, for in rheumatic fever after the first start off (which is due to a very abnormal rise of acidity, which may occur at any time, as it overpowers and obliterates the normal curves) the joints have their alkalinity very considerably diminished, and then the only effect of the alkaline tide or its representative will be to bring more uric acid to these joints, where it is further rendered insoluble and retained, increasing the irritation in the joints, and so raising the temperature in the morning (see previous remarks in chapter xv., on the causation of arthritis in gout, also uric acid filter experiments, chapter v.).

But there is still one important fibrous tissue of the body which we have not mentioned, and I was reminded of the possibility that it also may be attacked by uric acid by receiving a copy of a paper read by my friend Mr. Hope-Lewis at an inter-Colonial Medical Congress at Brisbane.

I gladly avail myself of his kind permission to reproduce it, as his suggestion as to causation is a most interesting one, and if he is correct we shall no doubt soon meet with other cases of which a similar explanation may be given.

The paper is headed "The Brain Fever of the Drama," and I reproduce it as sent to me :—

"Mr. President and Gentlemen,—I feel that in reading a paper under the above heading some introduction is demanded. I intend to give such an introduction, and at the same time to ask physicians to bear with a surgeon who has essayed to read a paper in the medical section. I by no means claim to have discovered a new disease. The case I am about to describe presented symptoms which were of an extremely interesting character and which called for a reasonable explanation.

"I have endeavoured to give such an explanation, and only regret that I am unable to quote several cases of a similar character. This may be rectified. There may be amongst my audience others who have seen cases of a similar character and who were unable to classify them.

"All medical men who for relaxation and pleasure go to the theatre will remember how at the end of the first act of a modern drama, or possibly in the second, the heroine receives a frightful shock at seeing the villain attempt to shoot or stab her lover. She thinks her lover is dead, and promptly has 'brain fever.' It is an invariable consequence of severe mental shock in the case of the heroine. Six or twelve months are supposed to elapse before the next act. The exigencies of the play demand an interval. The heroine is not ill all the time, but judging by the pallor of her face and the dressing wrap she wears in the next act, her convalescence has been delayed, and she always leans somewhat heavily on the rector's (her father's) arm. You do not have an opportunity of watching her illness. You only ascertain from the stage nurse that the heroine was desperately ill for some weeks and was unconscious, and that her mind was a blank from the time of the shooting or stabbing until one day she recognised that she was being kindly attended to by loving hands. Could it have been enteric? No. For years I had wondered what this illness

was. I had no opportunity of seeing the heroine after the shock —the curtain had dropped, except when the audience demanded her appearance before the curtain to receive its plaudits. In the next act she was convalescent. She had no sequelæ to guide one to a diagnosis except mental debility and fear of another appearance of the villain. That did not help one much. At last I met such a case in actual practice, and as it must needs be interesting to the profession I herewith narrate it.

"Mrs. A., aged 47, nullipara, married nineteen years, while apparently in her ordinary health received news by telephone one morning while at breakfast of the sudden death of her sister, who resided some eight miles away. She at once drove to her sister's house and was busily engaged during that day in duties connected with her sister's decease. She was deeply attached to her sister and felt the loss most acutely. She returned to her own home that night—a drive of about eight miles—and again next day drove to her sister's house and returned about 4 p.m. to her home, and went immediately to her bedroom with a splitting headache and lay down on the sofa. Both days were windy and cold for the time of year. On account of excitement she had taken hardly any food on these two days. She was a very nervous woman. On leaving the sofa to go to bed she fainted. I have no accurate account of the case for the next two days, February 2 and 3, but on February 4, her p.m. temperature was 103·8°. The chart gives a good idea of the progress of her complaint from that date." [I regret that want of space prevents my reproducing this chart, but it obviously differs from that of an enteric case in that the highest points, 104° F. to 105° F., are on the 7th and 8th days of illness; then it falls steadily till on the 20th to 22nd days it is between 100° F. and 101° F., then rises, reaching 103° F. on 26th day, keeps above 102° F. till the 30th day, then falls slightly below 102° F. to the 32nd day, when salicylate is given, and thence more decidedly to touch normal on the 39th day, and is below normal all the twenty-four hours on the 42nd day, and never rises again to 99° F.] "I saw the case in consultation with Dr. A. G. Purchas on March 4, the 32nd day of her disease, and her condition was then as follows: Her body had kept up its fat very well. Her pupils reacted to light sluggishly and were unequal. Her speech was slow and tedious in utterance. She had distinct '*tache cerebrale*' on the skin of her chest. Her tongue was red, clean and dry. Pulse thin and very rapid. She had the general appearance of a meningeal case. Her symptoms all through had a neurotic character—she would say she could not swallow; if

asked to turn round she would say she could not do so. She had great intolerance of light and sound. The room was kept dark and tan laid on the road near the house. She never had any diarrhœa, nor had she any spots. She had a great deal of flatulence and retching and had bilious green vomiting. She complained of aching in the legs, which were rubbed well and thereby somewhat relieved. She was very fat at the commencement of her illness, and at the end, though the arms and legs got thin, the abdomen and back kept fat. She was very flushed at times. She had fluid food principally, and water and nutrient enemata as necessary. She took very little food by the mouth. She lost her hair during her convalescence. My diagnosis of her case at the time of the consultation was that she was suffering from uric acid meningitis, and with Dr. Purchas's approval she took 20 gr. doses of salicylate of soda. There was a marked improvement in her general condition from this time. My opinion of this case is that it was a case of deposit of urate of soda on the meninges in the same way as that salt is showered on the serous surface of a joint. Dr. Purchas, who has had a very large experience in enteric cases, was certain it was not a case of typhoid, and was at a loss to classify the disease under any satisfactory heading. Doubtless many practitioners have had similar cases of a feverish prolonged attack following worry or serious and sudden mental shock, which have run a certain extended course to a successful termination, aided by or in spite of medicines. On questioning our patient and her husband it was ascertained that she had rheumatic pains prior to this attack for some considerable time, and that she was of a rheumatic diathesis. Her pains had been most severe in the posterior cervical muscles and fascia.

"Since observing this case I have come across another patient who some years ago had an illness of a very similar character to the one already described, and which also was caused by, or at any rate came on after, a severe mental shock. This second patient's hair turned white during the illness and has remained so since. Her age was 38 at the time of her attack. I am well aware that in describing this case as one of uratic meningitis I am treading on delicate ground, but since my personal acquaintance with Dr. A. Haig, commenced some five years ago, I have been keeping a sharp look-out for cases that one can fairly and reasonably classify as being due to the vagaries of that potent toxic agent. This, I submit, is a reasonable explanation of the cause of the illness before described. It is, no doubt, a rare

manifestation of the uratic storm,' but that uric acid causes migraine is now an established fact. In the case of migraine the position of uric acid is in the blood in greater proportion than it is in the large glands, joints or muscles, and with it in that position we get high arterial tension. If when in this condition we get an injury or a severe impression conveyed to any particular part my theory is that at that spot the uric acid storm bursts and expends its energy.

"I saw Mrs. A. just before leaving Auckland. She is now in good health with the exception of rheumatic pains about shoulders. She informs me that her mind was a complete blank from the second day on which she visited her deceased sister's residence until her convalescence commenced. She was not aware that she had been seen by me until she recovered."

Since these notes were in my hand, I have seen one case in the journals that made me think of the possibility of a similar causation, and if it had been under my care I should certainly have tried salicylates.

It is recorded in the *Lancet*, 1900, vol. i., p. 533, by E. F. Eliot, F.R.C.S., L.R.C.P.Ed., under the heading "Measles in a patient aged 18 years, complicated with meningitis and spinal myelitis; recovery." The cerebral trouble began on the fourth day of the rash with restlessness and teeth grinding, followed by convulsions. There was a scanty menstrual flow for a few hours on the previous day. Did this produce the collæmia, the uric acid of which was subsequently precipitated on the meninges?

Then two weeks later, when the temperature was 100·6° F., she was put on iodide of mercury alternating with quinine, iron and digitalis, and the temperature rose to 102° F. This alone would have raised, in my mind, the question of urate irritation, as these drugs would cause retention and therefore do harm in all urate irritation of fibrous tissues. That she eventually recovered is no argument against this, for, as we know, even acute rheumatism treated with acids may eventually recover. And measles, as we shall see further on, sometimes causes endocarditis. Was this a case of rheumatic meningitis precipitated by measles acting on the collæmic fluctuation produced by menstruation?

The future will tell us whether Mr. Hope-Lewis's most interesting and suggestive case is the key to the causation of a number of others; and I will conclude by suggesting that in meningitis of obscure origin, and that might conceivably be due to uratic irritation of fibrous tissues, salicylates should be tried, especially if the

administration of drugs that hinder the solubility of uric acid, such as iodide of mercury, iron, &c., appears to raise the temperature; and that I have acted on this myself will be seen in the description of figs. 69 and 70.

In Mrs. A.'s case abstention from food would cause collæmia, and then mental excitement produced a local fall of alkalinity, and precipitated some urate on the meninges.

These cases suggest also that it might be worth while to try salicylates in all cases of meningitis while waiting for the report of the bacteriologist, and even when microbes are present they may have acted merely as precipitants of urate.

As to season—acute rheumatism is not generally considered to present any definite relationships; and this is in accordance with what I have said, namely, that the attack is often the result of a severe cold or wetting, which may come at almost any season, and that this interferes sharply with the action of the skin, producing a marked fall in general alkalinity which overpowers the natural curves; the only thing that is necessary for acute rheumatism to result is, that at the time of the wetting the blood should contain a considerable amount of uric acid; and this collæmia would for the reasons previously gone into (fig. 4) be most likely to be met with in the spring and summer rather than in the winter, though severe exercise and perspiration would probably produce a temporary collæmia at any time, hence the very serious effects of a wetting following close upon these conditions of muscles and skin; and my friend, the late Dr. Eccles, read a paper at the West London Medico-Chirurgical Society (see *Lancet*, 1891, vol. i., p. 1433) showing that exposure to cold and damp after fatigue had important influence in the causation of rheumatic arthritis, and mentioned that his experience in over a hundred cases supported my views on the etiology of the trouble. After what I have said about fatigue (figs. 46 and 47) there should be no difficulty in completely understanding this sequence of causation (see also "The Practice of Massage," by A. Symons Eccles, p. 86). An arthritis resembling that of acute rheumatism can be produced without difficulty, or when present can be made worse, or a relapse can be produced in exactly the same way and with the same drugs as in gout; indeed, when one produces a relapse of gout by raising the acidity, the symptoms more often resemble those of rheumatism in that they affect several joints.

In my own person I have often produced symptoms which would, I have no doubt, have been pronounced rheumatism by anyone unaware of their origin.

In hospital cases it is often quite easy to see how diet, weather, or other independent sources of inflammation produce a rise of acidity (diminished alkalinity) and cause a relapse or aggravation of the rheumatic symptoms. Thus I have related * how, in a case under my care, a peridental abscess raised the temperature and produced a relapse of the rheumatism; and, as I can now see, but did not understand at the time, the action of the rise of temperature was probably aided and abetted by the quinine which I gave for his dental troubles (see Action of Quinine, fig. 10).

The treatment of acute rheumatism by lemon juice (combined, by the way, with plenty of hot water, blankets, and other sudorific treatment) has been supposed by some to be an instance of the cure of rheumatism by the administration of an acid, which would be strong evidence against uric acid causation.

But closer investigation hardly bears this out, for first of all the lemon juice is given with copious draughts of hot water, and the patient is in bed wrapped up in blankets, so that the skin is kept active, and there is a considerable excretion of acids by this channel. Secondly, the effects of considerable quantities of lemon juice on the acidity of the urine are very slight and transitory, as I can vouch for from my own experiments. On several occasions I took either strong infusion of lemon in hot water or strong doses of citric acid so far as I thought it safe to go (as citric acid in large doses is a powerful gastro-intestinal irritant), and the result as regards the acidity of the urine was very small (see previous remarks on the effect of taking cider, fruit, &c.); on one or two occasions, taken from hour to hour, my curves show that it rose a little at first; but the effect on total acidity of the twenty-four hours was little or nothing, and where the lemon is combined with copious hot water and blankets I have no doubt that the result is a fall of acidity and an increase of the alkalinity of the blood, which will account for the cures lemon has been said to effect in some cases. On this point Dr. Garrod says (*loc. cit.*, p. 200): "Dr. Fuller, on the other hand, found lemon juice do good in only three out of a series of twenty-nine cases, and ascribed to it the production of depression, griping and diarrhœa."

If it produces griping and diarrhœa this would bring about a fall of acidity of the urine and an increase of the alkalinity of the blood, and it might in some cases be of use in this way, just as a drug about

* Wood's "Medical and Surgical Monographs," February, 1890, p. 355.

which I have previously written, and which has been more in favour for the treatment of rheumatism than lemons, namely, colchicum. We now know also that griping and diarrhœa are merely a uratic irritation of the fibrous tissues of the intestinal walls (chapter x.). They represent the early and local action of the lemon juice where it raised the acidity; later on the intestinal irritation and diarrhœa would greatly lower the acidity and so produce depression.

Dr. Garrod says (*loc. cit.*, p. 201): "The extensive employment of colchicum in the treatment of acute rheumatism was doubtless owing to the supposed intimate relationship of rheumatism and gout." My own experience of colchicum showed that it produced considerable intestinal pain and irritation, and as the result of this a fall in urea and acidity, and the falling acidity brought about a plus excretion of uric acid. It should, therefore, according to my rule, be useful in all arthritic trouble which is due to uric acid. About its value in gout there is no dispute, and it is interesting to note, as I have previously remarked, that some have considered that in gout where it fails to purge it fails to do good, which is in favour of my argument. In rheumatism it has been, next to salicylates and alkalies, one of the best known treatments, and, if I am correct, it really acts as an alkali.

Of alkalies Dr. Garrod says (*loc. cit.*, p. 203): "The alkaline treatment renders the highly acid urine neutral or alkaline, without causing any increase in its quantity. The blood is found to coagulate more slowly, and the frequency of the heart's beats is considerably diminished." The reason why the urine is not increased and why the heart's beats are diminished is not difficult to understand, and I regard these as conclusive signs that the alkali has produced considerable collæmia, which, under the circumstances, we should expect; and Dr. Garrod goes on: "But the chief claim of this treatment was that it diminished the liability to cardiac implication, and in support of this claim the statistics of Drs. Dickenson, Senator, Chambers and others may be quoted, all of which show a considerably smaller proportion of cases with endocarditis and pericarditis among patients treated with alkalies than amongst those treated by other methods" (see also my cases of endocarditis further on).

It is interesting to remember that those who used ammonia in the treatment of acute rheumatism found that the urine remained acid and the pains severe, but that if alkaline salts of sodium or potassium were substituted the urine became alkaline and the pains were relieved (see Dr. Fuller, *Lancet*, 1862, vol. ii., p. 669;

and my paper on the "Action of Salicylates in Rheumatism," *Medico-Chirurgical Transactions*, previous references).

A similar claim of cardiac immunity has now been made for salicylates by Dr. Mitchell Bruce * and others, and if the cardiac troubles are due to uric acid it is easy to explain the action in both cases, but no other rational explanation has as yet been suggested. Both drugs have the same action on uric acid, but otherwise they have little in common, and it is more than doubtful whether either affects the microbes.

As regards salicylates, I have pointed out that the excretion of urate during the first few days of their use in acute rheumatism is enormous; the excretion is not only absolutely large, as 26 gr. in the twenty-four hours, but uric acid bears an abnormally large relation to the urea excreted along with it, *e.g.*, 1—17 in the case which excreted the 26 gr. and 1—14 in the case of a boy of 14 under my care (see fig. 68).

This figure shows an enormous excretion of urate in the first twenty-four hours, the absolute quantity being upwards of 26 gr., but, taking urea as our standard, only 16 gr. of urate were formed on this day (in the relation 1—35). Therefore about 10 gr. of urate came from some source other than formation, and it was this urate which caused the arthritis, and so with its removal and excretion under salicylate there was a marked fall of temperature and amelioration of all the symptoms; and the slowing of the capillary reflux (from 4 before salicylates to 8 or 10 after) and the increase in the granules in the blood (from 1 to 30 red cells before and 1 to 1 after salicylate), as recorded in previous chapters, also tell us of a large excess of uric acid in the blood.

This urate was present in the joints as a urate in colloid form, and if it had remained untreated or otherwise unremoved, it might have gone on to the deposition of the biurate, crystals of which might then have been afterwards found in the tissues; but as a rule in acute rheumatism it does not reach this stage, and so crystals are not found so frequently or to such an extent as in gout (see also previous remarks on Dr. Mordhorst's researches in chapter v.).

On November 8 the excretion of six hours of the alkaline tide period (all that could be got before treatment) was multiplied by four and counted as a day. This accounts for the slight plus excretion of urate and the low acidity. If the whole twenty-

* *British Medical Journal*, 1890, vol. i., p. 491.

four hours could have been collected, urate would, no doubt, have been far below urea and acidity much higher, this condition of things corresponding with more or less complete absence of uric acid from the blood and the existence of acute arthritic symptoms from its presence in the fibrous tissues.

On November 10 the urine was lost by mixture with another specimen, and on November 11 we see that urate is below urea in spite of 80 gr. of salicylate in the twenty-four hours. Most of the available urate had been removed on the previous days, and it had

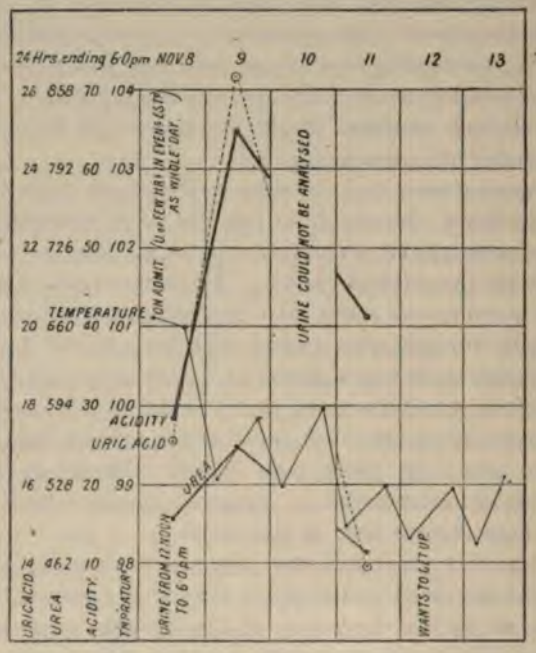

FIG. 68.—CURVE OF EXCRETION OF URIC ACID IN ACUTE RHEUMATISM UNDER SALICYLATE OF SODIUM.

nothing to act upon, but with this the temperature is normal and the patient convalescent, and next day he wants to get up.

We have here, as regards the excretion of uric acid and the fall of temperature, a mere reproduction of fig. 62.

Compare this with the excretion of urate under salicylate in physiological conditions (fig. 8). The curves are seen to be very similar. The only difference is in the absolute quantity.

Now, in accordance with my premise that uric acid is not

formed in greater proportion to urea than 1 to 35 (see my Facts and Deductions in chapters ii. and iii.), in both the above cases about half the uric acid excreted under salicylate must have come from some source other than the formation of that day, and I have suggested that this extra urate came from the joints, and that its removal accounted for the subsidence of pain, irritation and temperature, and, as I have also pointed out, the value of the salicyl compounds in acute rheumatism is proportional to their power of dissolving and eliminating uric acid (*Medico-Chirurgical Transactions*, vol. lxxiii.).

In this connection one often hears people speak of uric acid as if it were so much sugar, and as if 10 gr. of it could be introduced or formed, passed through the blood, and excreted in the urine any day, almost any hour, without producing any effects.

Many years of sorrowful experience have completely convinced me that this is very far from the truth. Even one-half of this quantity, if added on to the ordinary daily excretion and passed through the blood in a few hours, will cause very distinct signs of its presence, *e.g.*, slow capillary reflux, high blood pressure, headache, mental depression, dyspepsia, congestion of the liver; and even a fraction of this amount, when driven out of the blood into the joints and other tissues by drugs taken to clear the blood and relieve the above symptoms, may produce pains in the joints which are decidedly uncomfortable, and, if continued for more than an hour or two, may in turn require to be relieved by salicylates.

I must say that I do not envy the position of any man who has from four to five times this amount of uric acid in his joints irritating them. I have often had quite as much pain as I could bear with smaller quantities (see fig. 74).

Do not let me be misunderstood. I am quite aware that any gouty man may have more than 20 gr. of urate in one single joint, and may suffer but little inconvenience from it; but then such urate is not in solution, but deposited and lying quiet in the tissues. The condition I am speaking of is that of a man who has 10 gr. to 20 gr. of uric acid driven rapidly out of his blood into his joints, where it remains in strong solution, or colloid form, and with full powers of causing irritation in all the tissues with which it is in contact; such irritation leads on to an inflammatory effusion, pressure and tension, and the painful arthritis of acute rheumatism is thus accounted for.

Some years ago Dr. E. Pfeiffer, of Wiesbaden, told me that he had for purposes of experiment injected urates in suspension under his skin, and that they caused pretty decided local irritation.

He then proceeded to take acids and alkalies alternately, and he found the alkalies increased the irritation produced by the urates, but the acids diminished it, and he evidently seemed to think that this was in direct contradiction of my assertion that solvents relieve the pain of arthritis, while drugs which cause retention increase them.

But Dr. Pfeiffer's urates were in suspension, and the alkalies increased the pain by getting some of them into solution, and the acids relieved the pain by preventing their solution (see Dr. Mordhorst's results, quoted in chapter v.).

The urates that cause acute arthritis are in solution or colloid form in suspension, and not crystalline, and they are deposited later on as crystals, and are then comparatively unirritating. We must bear the point in mind, as it is quite possible that the getting of old urate deposits into solution, as occurs in ordinary old age and the decline of life, may for a time increase the pains.

And this also may to some extent explain the action of drugs of the iodide, sulphur and cannabis indica class in relieving chronic gout and rheumatism.

In chronic rheumatism, associated with debility, there is an almost continual excess of uric acid passing through the blood, and every rise of acidity increases the joint irritation; in this case the pains will be worse at night.

But if there are considerable urate deposits, and the getting of these into solution causes increase of pain, then the pains will be worse in the morning, and then stimulating drugs or diet (such as pure meat diet), which prevent the re-solution of these old deposits, will relieve the pains.

Small deposits of urates may undoubtedly lie in the tissues for years and give almost no sign of their presence, but if you administer an alkali, which begins to get the deposit in solution, there will also begin a more or less marked local irritation round the seat of each deposit, and this is exactly paralleled by the way in which the chronic arthritis called "rheumatism" is liable to increase on first giving alkali. This increase of trouble often leads those who do not understand it to consider that the treatment is doing harm and should be given up; it is really, however, merely a sign that the solvent is beginning to get some old deposits into solution, and that the dose should be increased to hasten that solution and aid elimination from the body. In many cases we can see exactly where there have been deposits from such irritation beginning when alkali is given—it may be in the nose or throat, it may be

in the eyelids, it may be in the muscles or bones or the teeth, but wherever alkali appears to start an irritation you may be sure that there has been a deposit there which up to the present time has been lying quiet, producing no results. You can put an end to this trouble either by giving up the alkali or by increasing it, and no doubt the latter course is the better, as only by that means do you obtain complete elimination of the uric acid from the body, and once these deposits have been cleared out the future administration of alkali will never produce any similar effects, showing that it was not the alkali, but the condition it met with in the tissues which produced the trouble.

Acids do harm in acute rheumatism, and cases so treated take a longer time to get well than those which are given only mint water; also, as observed by others, ammonia, which keeps the acidity of the urine high, does harm, while soda and potash, which lower the acidity of the urine, do good, and if we are dealing with uric acid as a cause of rheumatism these facts require no further explanation. An arthritis practically indistinguishable from that of acute rheumatism, and an endocarditis also indistinguishable, have been produced, as previously pointed out (*Practitioner*, 1891) by giving and injecting acids respectively (see also cases recorded further on). We must not forget either that, as Sir A. Garrod had shown, urate of ammonium is insoluble, and that ammonium compounds may act like those of lead, mercury, and other metals in clearing the blood of uric acid and precipitating it on the joints. Hence they relieve headache and depression, and are often used for that purpose.

I have also pointed out that acute rheumatism is a self-curing disease, that the pain, sleeplessness, failure of appetite and digestion, and the absolute rest which the pain enforces, bring about at last a fall in urea and acidity, and that acidity is still further reduced by a considerable excretion of acids in perspiration; so that when the alkalinity of the blood has thus to a considerable extent been restored, the urates are dissolved out of the joints and excreted, and the fever comes to an end, with the production, however, of considerable collæmia, anæmia, and debility; hence the alternation of rheumatism with anæmia so common in girls and young women (see chapter xii. and fig. 59).

More or less headache and slow high-tension pulse are also the common signs of this uric acid collæmia, and Dr. Garrod (previous reference, p. 64) gives tracings of such a pulse in convalescence, while, as I have previously pointed out, Dr. Stephen Mackenzie says migraine alternates with acute rheumatism, and he deduces

from this the suggestion that both diseases are nerve storms; but migraine, we know, corresponds with excess of colloid urate in the blood and the rheumatism which alternates with it, with the presence of the same urate in the joints, and both can be cured or prevented by the uric-acid-free diet. It is interesting to note, as pointed out by Dr. Latham (*Lancet*, 1901, vol. i., p. 999), that Trousseau and Remak found that rheumatoid arthritis in women is often preceded by migraine.

Acute rheumatism may be produced by anything that causes a sharp rise of acidity or fall in the alkalinity of the blood at a time when there is a considerable supply of urate in the circulation (collæmia), but if there is little urate a rise of acidity may produce little effect, hence those who eat most meat (see Bouchard*) and drink most beer, and have in consequence most uric acid stored in their bodies, will be most likely to have occasionally considerable collæmia, and when exposure to cold and wet or the sudden onset of any fever supervenes upon this, acute rheumatism may result.

Now, tonsillitis is very commonly a forerunner of rheumatism, and, indeed, some have claimed it as a part of the rheumatic process, but if this is the case it must often be its only sign, as there may be no other symptom of rheumatism either before or after it.

But tonsillitis is, in my experience, very often associated with conditions of fatigue and over-exertion, and these are just the conditions which bring about considerable collæmia, and when acute tonsillitis supervenes upon this, it is hardly to be wondered at that we should have some joint pains or acute rheumatism.

I do not deny that pharyngitis or tonsillitis may originate in a gout of the fibrous tissues and glands of the throat, and I know that this often is its cause; but I want to point out here that any rise of temperature, even a traumatic temperature, may under certain conditions produce arthritis.

Influenza, again, with its rapid rise of temperature, generally produces some pain in joints and fibrous tissues, and several cases have been recorded in which it has produced endo- or pericarditis.

A fever, however, has a double action, for supposing that at the time of its onset there is no collæmia, it will not produce rheu-

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* "Leçons sur les Maladies par Ralentissement de la Nutrition," p. 241, and this slackening of nutrition, I remark, is the result of the collæmia, not its cause.

matic symptoms, but as the fever rises the acidity of the urine rises also, and the alkalinity of the blood is diminished, the excretion of uric acid falls below formation, and while the fever lasts a considerable amount may be held back in the body, in the liver, spleen, and elsewhere; then when the fever comes to an end and the acidity falls, more or less collæmia will result from the washing out of this stored uric acid. On this let us suppose there supervenes a sharp rise of acidity (from diet, exposure to cold, or the inflammation of any organ occurring as a complication), and acute rheumatism, more or less severe, will result; that is the explanation of the rheumatism that follows scarlatina and other fevers, as measles (see Sansom, quoted by Dr. Garrod, p. 182, and paper read at the Royal Medical and Chirurgical Society on "Measles as a Cause of Endocarditis," *Lancet*, 1891, vol. i., p. 880), and compare this with my remarks on the effects of measles on the urine in a case of morbus Brightii (chapter xiii.). The rise of acidity in the fever which cleared the blood of uric acid might, under certain conditions, have driven that urate into the fibrous tissues of the joints or heart; the clearing up of the collæmia freed the capillaries of the kidney, and profuse diuresis and removal of anasarca resulted. We here see the relationship of nephritis and the chronic collæmia which accompanies it, to the disease of the aortic valves not rarely found along with it in the *post-mortem* room (see Dr. Norman Moore, *St. Bartholomew's Hospital Reports*, 1887, pp. 290 and 291), though no doubt the high blood pressure of the collæmia will put a strain on the aortic valves.

There is evidence to show that the acids of beer and wine and the excessive formation and introduction of urates in a highly nitrogenous diet play the same part in rheumatism that they do in gout, only in acute rheumatism, where the onset is violent and the sharp rise of acidity is probably due to the action of several causes working concurrently, it is difficult to apportion to each its actual share in the result; but it is known to be dangerous to give meat, beer, &c., too soon after an attack, and the way in which they produce a relapse is obvious.

In rheumatism, just as Sir A. Garrod observes to be the case in gout, the effect of giving iron is to bring about increase of pains and rise of temperature; and in a patient suffering from anæmia under my care, who had had acute rheumatism, it was found to be quite impossible to give iron on account of the rheumatic symptoms it produced, and in several cases of chronic rheumatoid arthritis I have had to give up the administration of iron for the same reason, and if the joint symptoms in all these cases are due to chronic irritation by urates, there is no difficulty in understanding the facts.

With regard to tonsillitis, mentioned above, there are several points of great interest: for not only has tonsillitis often been considered to be related to rheumatism, but Le Clere (*Journ. de Méd.*, January, 1899) points out that it may precede attacks of gout in exactly the way that it has more often been observed to precede rheumatism.

And this observation is exactly what I should expect, for I am certain that many acute inflammations of pharynx, tonsils, larynx and trachea in arthritic subjects are just as certainly due to uric acid as the arthritis which may or may not follow them, and my own case, given in fig. 74, is as conclusive proof of this as anything can be.

But the notes of the following very interesting case which I owe to the kindness of my friend Dr. C. Gayford, seem to show not only that a tonsillitis may have a uratic origin, but that a similar uratic irritation in fibrous tissues may spread from the throat to the glands of the neck, causing inflammation and marked enlargement of these structures, and that the irritation thus set up may continue for many months, and is in no way relieved by tonics and change of air, which would not aid the elimination of uric acid but the reverse; while the irritation clears up and the glands diminish on a change of diet, which stops the introduction of uric acid and provides for its elimination.

Dr. Gayford also observes that the original acute trouble in the throat was relieved by salicylates just like a gout or rheumatism, while the enlarged glands which were left behind increased and diminished on several occasions in exact relation to the animal flesh in the diet.

Dr. Gayford had, for some years before this case came under his care, taken an interest in my work on the influence of diet and drugs on uric acid, and in his letter telling me of the case he says that my investigation turned his attention to the possibility that gout was at the bottom of his patient's trouble and that diet might relieve it.

"G. G., aged 20, consulted me on April 18, 1894, suffering from general malaise, sore throat (tonsillitis), anorexia, the temperature 101° F., pulse 120.

"I ordered him home and to bed, and gave him a mixture containing sodii salicylas and bark, with a powder pulv. hydrarg. subchlor., pulv. ipecac. co. āā gr. iii. statim.

"The next day his temperature was 99° F., pulse 96, headache less, but anorexia still continued.

"On the 21st, he first called my attention to swellings on both sides of his neck, the glands in both anterior and posterior tri-

angles being enlarged. He was very prostrate and ill, though the temperature had fallen to normal.

"24th, he had rallied somewhat, the pulse being stronger, the temperature subnormal.

"The glands were larger, tender to the touch, the skin was tense over them. A string of enlarged glands, extended from just below the ear down through the whole length from base to apex of the anterior triangle, and from apex to base of the posterior, deep into the root of the neck and were felt in both axillæ; the largest of them was as large as a pullet's egg. They were separate and mobile, but continued very tender to the touch.

"There was no enlargement of either liver or spleen, nor were any joints affected. The temperature continued normal or subnormal, there were no night sweats.

"There was continued pallor, profound prostration and anorexia, evidence of deep-seated constitutional disturbance.

"Being a relative, naturally I felt considerable anxiety at his condition. He, however, gradually mended, and in about ten days was able to get about again, though continuing to look ill. He was soon tired out and unfit for much exertion.

"The glands were less tender, but continued enlarged, hard and dense and freely movable one upon another; there was no sign of matting together. The question which arose in my mind was, were they tubercular or not?

"The condition persisting on the 21st of May, a month after the attack set in, I took him to see Mr. Butlin, who after carefully examining him told me he feared there was not much room to doubt that they were tubercular, and he advised that he should go away from England to South Africa, or some other warm, high and dry sub-tropical climate and remain abroad. The glands enlarged were so numerous and so deep seated that operation was out of the range of practical treatment.

"As there were strong reasons against my relative's leaving England permanently, he suggested that a prolonged voyage in the Mediterranean to and from South Africa or New Zealand might result in so far re-establishing his health, and reducing the number of glands involved, that then operation might become practicable.

"He went for a prolonged cruise in the Mediterranean and came back greatly improved in health; he had gained weight considerably and looked robust, but the number of glands had not decreased nor were they smaller.

"Hence we waited on events, treating him meanwhile with good

food, open-air exercise, iron, strychnia, arsenic with quinine; calcium sulphide tabloids, gr. i., were taken frequently and over an extended period of time; tabloids of bone marrow and spleen were tried; externally ung. iod. cadmii was ordered as an inunction, but in spite of all there was no further reduction either in the size or numbers of the glands.

"I had frequently thought over the question of tubercle, either actually present or imminent, and as the autumn came on I felt that this question was a pressing one, for the danger of spending the winter and spring in England to one seriously threatened with tubercle was very real.

"His family is not tubercular at all, no member of it excepting a half-sister of his father—and she an only child of the marriage, and her mother's family were consumptive—having suffered from phthisis. In this case there was no evidence of the presence of tubercle in an active form. His ancestors on both sides were gouty.

"After reading Dr. Haig's book on uric acid, the query arose Was it a case of rheumatic tonsillitis followed by enlarged glands?

"In November, 1894, I determined to try what a radical change in his diet would do; accordingly I ordered him a simple milk diet, prohibiting meat in any form.

"He took to it, taking fully five pints of milk a day in various ways, for several weeks supplementing it with bread and farinaceous foods and fruit.

"He put on flesh, and to my delight the glands soon showed unmistakable evidence of resolution. Just before Christmas there was only one to be felt at all, situated in the apex of the right posterior triangle just where the sterno-mastoid is overlapped by the trapezius.

"During the festivities of the Christmas season he was once tempted to take a little turkey at dinner; two days afterwards when I saw him the glands had again enlarged on both sides, on the right more than on the left.

"Resuming his milk diet they again disappeared, the slightest indulgence in meat diet always being followed by enlargement, and this was a matter of constant and repeated observation.

"For fully nine months he kept steadily to a milk diet, with the result that his health was completely re-established and the glands disappeared. He then gradually resumed an ordinary mixed diet, the quantity of meat he took being strictly limited, for he had learnt to know how much he could take.

"Since the middle of 1895 his health has been uniformly good.

He is a Volunteer and gladly takes up his drill duties, and is as fit as any of them for long marches and field operations. During his holidays he has taken long tours on his bicycle or long boating trips up the river.

"He has been actively engaged in business, and only quite recently (1898) he made a proposal to insure his life in a first-class life office, and after giving the medical examiner all the facts as to his glandular trouble of four years ago he has been accepted at ordinary rates. The medical examiner for the office has all along been cognisant of the case, and he at first advised operation before Mr. Butlin was consulted. The last item of interest in this interesting case is the marriage of the patient. Reviewing all the facts of this case, it seems to me clear enough that it was one of rheumatic tonsillitis and adenitis. The acute stages of both yielded readily to the action of sodii salicylas, but the consequent chronic hyperplasia persisted for months with but little evidence of progress towards recovery, though various forms of treatment were tried. It was not until the radical change in diet was instituted that this condition yielded, and then the resolution was both prompt and complete."

In support of his argument that the glandular enlargement was due to rheumatism, Dr. Gayford refers to the writings of various authors on enlargement of glands, and also to a paper by Dr. Still on "A Form of Joint Disease in Children associated with Glandular Enlargement," read before the Royal Medical and Chirurgical Society, and reported in the *British Medical Journal*, 1896, vol. ii., p. 1446.

Among Dr. Still's cases was one in which there was enlargement of the spleen as well as of the glands, and he quotes Dr. Still as being "inclined to the view that the disease was infective in nature."

Dr. Gayford also mentions that while in his relative's case there was clearly no tubercle from first to last, he had seen other cases in which he believes that tubercle has become engrafted upon such enlarged glands or similar rheumatic irritation of the throat, thus repeating the suggestion of Dr. Buckler with regard to the lungs, which I have quoted and supported in chapter ix.

I shall continue to believe an arthritic fever to be due to uric acid so long as it is relieved by solvents and made worse by precipitants; but I do not doubt that microbes and their products may act as precipitants and produce a uratic arthritis.

So long as the arthritis is relieved by heat and alkalies, which

are solvents of uric acid, but have never been claimed as antiseptics, so long as salicylates cure the arthritis in fever and in cold climates, but fail to do good in hot ones, so long shall I believe that these drugs act as solvents of uric acid merely, and not as antiseptics at all; if they are antiseptics, why will they only act in cold climates?

Diet, again, though not an antiseptic, will do infinitely more for all forms of rheumatism than any drugs, as Dr. Gayford's case well illustrates.

It shows, as clearly as anything can be shown, that the glandular enlargement in G. G. was not tubercular, was not infective or contagious, and was due to the irritation of urates, which, till the diet was altered, were being constantly introduced in the food.

Then a large proportion of the drugs used would have the effect of driving urates into the tissues instead of dissolving them out and removing them, and hence would rather keep up the irritation than remove it.

Dr. Gayford clearly wishes to raise the question whether many other glandular enlargements of obscure origin are not due to rheumatic irritation, that is, to uric acid, and I should myself also take this view most strongly, for I have not only suggested that uric acid may irritate any and every fibrous tissue in the body, but that cancer itself may take origin in the irritation so produced (chapter x.).

Thus Dr. Gayford's patient might have suffered from cancer, taking origin in the irritated throat or glands, or if he had been exposed to a large dose of tubercle bacilli while in a condition of low combustion and unable, as I have suggested, to burn them up and destroy them, these might have found entrance through the irritated throat to the enlarged glands.

In either of these cases he might have lost his life, but so long as the irritation was only due to uric acid a change of diet removed it, and he was no longer a possible prey to cancer or tubercle.

I think it highly probable that, as Dr. Gayford suggests, many forms of glandular enlargement, with or without splenic enlargement, and with anæmia or leucocythæmia, will be proved to be, like splenic leucocythæmia, which I have mentioned above and about which I have quoted Raynaud's parallel opinion, mere diseases of the blood and blood glands produced by uric acid, in a word, their reaction to excess of uric acid, the anæmia being due to its circulation effects, which I have already explained, and the glandular and splenic enlargement to its local irritant effects.

The glands in such cases generally enlarge at the time of a rise

of temperature, this indicating a gout of the fibrous tissues of the glands; and a similar enlargement of the spleen does, as we know, occur in malarial fever, and I have already suggested that in those who are free from excess of uric acid, malarial fever either does not occur or is greatly modified (chapter xii.).

I have seen at least one or two cases of arthritis in which there was enlargement of neighbouring lymphatic glands, and this did not lead me to think of microbic infection, but I concluded that uric acid had irritated the fibrous tissue in the glands as well as that in the joints, and for records of cases in which tonsillitis was associated with enlargement of cervical glands see article by Mr. J. Snowman, *British Medical Journal*, 1898, vol. ii., p. 1744; and in the following number a letter from Dr. G. Mahomed, who mentions in one case the presence of "neuralgic-gouty habit."

Dr. Gayford tells me that he has seen several cases which directly support the theory that tubercle bacilli have found entrance through a similar rheumatic throat to similarly irritated glands, the patients eventually developing tubercle in the larynx, the neck glands, and the lungs; and the case of phthisis I mention in chapter ix. came of a very gouty family, and had, as I suggested, rheumatism in his shoulder and mitral valves.

These cases are suggestive merely, but Dr. Gayford's case is far more than suggestive or theoretically interesting, for it tells us in no uncertain language that extensive enlargement of glands in gouty subjects and others (I think many others) may, even though believed to be tubercular, be cured by the diet treatment of uric acid. I have also seen several cases of enlarged neck glands following febrile sore throat, in which salicylates followed by diet have very obviously quickened the disappearance of the glands.

I have long regarded tonsillitis, pharyngitis, post-nasal catarrh and resulting adenoids as rheumatic, and have cautioned mothers and others concerned to diminish meat and cut off tea, with good results. I have regarded all the chief forms of anæmia as representing the effects of uric acid on the blood, and we now seem to be coming in sight of the real connection between malaria, leucocythæmia, enlargement of the spleen and of other glands as well, and this knowledge may presently give us as much power over these glandular enlargements as we already have over the blood.

The effect produced by uric acid will vary in different individuals just as do those of wounds and setons; some will have great changes in joint structures and fibrous tissues, others little; some will have great enlargement of glands with an attack of tonsillitis,

others little, or it quickly goes away; but these differences do not show that the irritant is not uric acid, and when the irritation is promptly put an end to by salicylates or a uric-acid-free diet, that is satisfactory evidence of causation.

Age is an important point, because it furnishes probably the chief cause of the difference between gout and rheumatism, and I have already pointed out that the condition of the joints is different in the young and in the old.

Sir A. Garrod has shown that the tissues of joints are not only less vascular but less alkaline than the blood and other tissues, and there can be no doubt that as life goes on, as the arteries become tortuous and degenerate, and as activity of mind and body lessens, the circulation in these joints becomes less and less well maintained, and their alkalinity continually reduced, so that slighter and slighter causes will suffice to render them neutral or even acid. It is this sequence of events probably more than any other which precipitates uric acid and produces the stiff and painful joints so common in the aged, even where no rheumatoid changes are visible.

So that while the joints of the young are both more alkaline and better able to maintain their alkalinity, this may nevertheless be overcome by a great and general fall of alkalinity, which affects many joints at once and is due to a powerful external cause (acute rheumatism).

In the old, on the other hand, the joints are less alkaline and have also diminished power of maintaining their alkalinity, so that comparatively trivial external causes (a slight injury, a little extra exertion, cold, &c.) may diminish the alkalinity of a given joint, especially those of the hands and feet, where the peripheral circulation is feeble, and gout results.

It is probable that uric acid collæmia itself may, by obstructing the vessels, render the circulation in the extremities less active, and so aid in diminishing the alkalinity of certain joints, in which the uric acid from the blood is eventually collected and deposited.

But age has an important influence on another factor of uric acid arthritis, namely, the absolute quantity of uric acid that is formed, for while in adults urea is formed in about the proportion of 3·5 gr. per pound of body weight per day, and uric acid in its natural relation of 1—35 would be about ·10 gr. per pound per day, in a child of three or four years old urea may be as much as 9 or 10 gr. per pound, and uric acid ·27 to ·3 gr. per pound.

A child or young person is thus by nature placed in the position of an adult who eats largely of meat. The daily formation of uric

acid is relatively large, and uric acid collæmia and arthritic irritation, so far as they depend on formation for supplies, are correspondingly easily produced (see also p. 236).

When young persons, who have naturally this extensive nitrogenous metabolism, increase it by eating largely of meat, meat extracts, juices, and essences, the introduction and formation of uric acid must both be great, and the possibilities of resulting mischief considerable, and it is little wonder that, as pointed out by Bouchard (previous reference), children fed on meat and meat extracts should often suffer from gastro-intestinal derangements, skin diseases (see chapters x. and xi.), and early migraine, and that rheumatism and its most serious manifestations should come early.

If I have escaped from migraine (uric acid headache) by reducing the introduction of uric acid, it is no very extraordinary thing that children whose naturally large nitrogenous metabolism has been increased by inordinate indulgence in meat should suffer severely, and these facts carry their own moral.

Age also influences one or two minor points, which may at times have considerable power in precipitating rheumatic (uric acid) arthritis.

One of these is the fact often insisted upon by a teacher of whom I have the most kindly recollections, the late Professor Rolleston, of Oxford, that small animals have necessarily much more surface in proportion to bulk than large animals, for surface increases as the squares, but bulk increases as the cubes of the dimensions. Hence external influences, such as wet and cold, will have proportionally greater effects on small than on large animals, and wet and cold, as we have seen, raise the acidity of the urine and diminish the alkalinity of the blood by checking the excretion of the skin (Garrod). It follows that rises of acidity from this cause will be greater and more powerful in the young than in the old.

Another point is that in children and young persons (probably in consequence of their more active metabolism) slight disturbances will produce great increase of temperature, and rise of temperature means rise of acidity, the two things (fever and acidity) being co-resultants of increased metabolism. Hence the extraordinarily rapid development of girls at the age of thirteen (fig. 59) may account for their liability to acute rheumatism about that age, as well as to chlorosis and anæmia a few years later.

Thus young persons are, from the action of natural causes, often liable to have considerable collæmia, and wherever external cold or febrile disturbance supervenes upon this, a powerful rise of acidity

will drive the uric acid out of the blood into the joints and other tissues, for these tissues no doubt share largely in any general fall of alkalinity.

A child with gastro-intestinal disturbance and loss of appetite has a headache and slow pulse, the signs of collæmia. On this there follows exposure to cold and wet, a sore throat, a peridental abscess, or other cause of febrile movement, and the resulting fall in alkalinity quickly produces a multiple arthritis with endo- or pericarditis, and changes the picture to that of acute rheumatism.

In this way the production of acute rheumatism may be completely accounted for by the action of causes that are to be met with every day, and in these meat-eating days the wonder is that any children should escape an attack; but it is fortunately necessary that several causes should act together, and this can only occasionally be possible.

Thus collæmia means a large excretion of urate, and where this has gone on for several days the amount in circulation will be reduced. Again, gastro-intestinal disturbance means diminished metabolism and lessened formation of urate, so that unless external cold or febrile movement supervene at an early date there will not be enough urate to produce the most severe effects on the fibrous tissues. I shall now quote three cases which were under the care of Dr. Savill at the Paddington Infirmary, the notes of which he has very kindly placed at my disposal, as they serve to illustrate several of the most important points I have mentioned.

Case I.—John G., aged 69, coachman. Admitted February, 1886. Rheumatism and gout badly for years in knees and ankles. First severe in 1853, in right hand, then in feet, and then general.

Father asthma and slight rheumatism, died at 82 years of age.

On admission, February, 1886: Urine 1018. No albumin.

March, 1886.—Much better, gets about fairly well; is taking cod-liver oil.

April, 1886.—Urine 1020. Cloud of albumin.

October, 1886.—Left hip painful, 2 in. shortening and joint disorganised.

November 30, 1886.—Giddy and headache in morning two or three days ago; better now.

December, 1886.—Much pain in hip. Hands show marked rheumatoid change and distortion of fingers.

1887.—Much the same, giddy on exertion. Pulse compressible, arteries thick. Urine 1008. Trace of albumin.

1888.—Many joints affected; marked rheumatoid changes in hands, elbows, shoulders, knees, and left hip.

1889.—Urine, occasional albumin, joints somewhat relieved by soda baths.

1890.—Pains vary with weather, and are worse in east wind. Can walk with the aid of a stick.

August, 1890.—Urine 1014. Albumin $\frac{1}{6}$. Anasarca of both legs, petechiæ on right.

November, 1890.—Pulse tension plus. Urine 1016. Petechiæ on both legs.

January 6, 1891.—Urine 1012. Albumin large trace.

January 30.—Diarrhœa and collapse. Died 9.15 p.m.

Post-mortem.—Body exceedingly well nourished. Rigor marked. Petechiæ on legs numerous.

Heart.—17 oz. Left ventricle large. Valves normal. Atheroma of abdominal aorta. Arteries tortuous and thick.

Lungs.—Emphysema and congestion.

Liver.—40 oz. Hobnail, cirrhotic.

Kidneys.—2½ oz. each. The right contains a cyst as large as a hen's egg. Cortex much reduced. Capsule adherent, surface granular.

Spleen.—5 oz., capsule thick.

Joints.—Deposit of urate of soda in cartilage of metatarso-tarsal and metatarso-phalangeal joints of right great toe.

We may sum up the *post-mortem* by saying gout with extensive rheumatoid changes, granular kidneys, cirrhotic liver, hypertrophied heart, and degenerate vessels.

Case II.—Charlotte W., aged 62, laundress. Clinical paper headed "Progressive Chronic Articular Rheumatism."

Father died at 70 of rheumatism. Mother died at 68 of asthma.

Patient had rheumatism first in toes, then in ankles, and then knees.

Admitted July, 1888. An anæmic woman, with enlargement of second phalangeal joints affecting the bone ends. Metacarpo-phalangeal joints also enlarged. Some tilting of fingers to ulnar side.

Left knee much enlarged; very tender on the inner side; brawny œdema of lower part of joint.

Heart.—Systolic murmur at apex and left base. Pulse 90. Artery thick, tense, tortuous.

August, 1888.—Pulse tracing to-day shows a large first wave high up. Urine, albumin ½. Bullæ forming on ankles.

September, 1888.—Cough and dyspnœa increasing. Died on 21st.

Post-mortem, September 22, 1888.—Body somewhat emaciated; rigor absent.

Heart.—18½ oz. Left ventricle hypertrophied. Aortic valve incompetent, with thick attached borders. Mitral valve slightly thick.

Lungs.—Contain infarcts, with general congestion and œdema.

Kidneys.—Numerous cysts, small, hard, granular. Right 3 oz., left 4 oz. *Liver.*—57 oz., nutmeg, with fatty degeneration.

Joints.—Copious deposit of urate of soda, much erosion of cartilage, tissues around thickened and infiltrated with deposit.

This, then, is another case of gout with extensive rheumatoid changes (diagnosed during life as "Progressive Chronic Articular Rheumatism"), and granular kidneys, but to these are added disease of aortic valves, and the condition of the lungs and liver was no doubt secondary to this.

CASE III.—Mary C., aged 65. Dressmaker. Admitted January, 1890. Case headed "Progressive Chronic Articular Rheumatism," with gouty history.

Father delicate, suffered from rheumatics in early life. Mother and one sister died of diabetes. One brother has rheumatism. One brother has gout.

Patient had inflammation of the kidneys when a girl, and in 1885 an abscess on the face, which discharged for thirteen months. Note the way in which all these diseases, gout, rheumatism, diabetes and Bright's disease, come together in a family.

The rheumatics came on twenty-seven years ago when she was pregnant, and got worse after her confinement. First came in her ankles and feet. Did not finally give up work till eight years ago. Is now able to get about on crutches.

Present condition.—Metacarpo-phalangeal joints seem most thickened and distorted, and their movements are very limited. But all the joints—elbows, knees, ankles—are thickened and distorted, and more or less fixed. Ankles seem to be completely so.

Hips and shoulders least involved. Spine movements impaired. Skin pale and smooth, not glossy. No fluid in any joint. Heart sounds normal but feeble. Lungs, emphysema, but natural otherwise. Urine normal.

March, 1890.—Gets more helpless.

May, 1890.—Urine pale, cloudy, acid, 1028. No albumin.

August, 1890.—Lin. terebin. relieves pain.

December, 1890.—Great pain in right arm.

Urine 1022, acid, cloudy. No albumin.

March, 1891.—Suffers a great deal from pains, but they are lessened by lin. terebin.

May 19, 1891.—Face pale. Pain between shoulders and across abdomen. Breathing laboured. Bronchitic sounds front of chest. Bronchial breathing over right upper lobe, and crepitation on both sides of back. Sputum thick, purulent, not rusty.

Slightly better the next day (May 20), but there is bronchial breathing all over left back now.

She died on May 24.

Post-mortem, May 26.—Pleuræ, a few old adhesions both sides.

Heart.—12 oz., substance firm. Aortic cusp of mitral valve slightly thick.

Lungs.—Right, 22 oz.; left, 23½ oz. Considerable consolidation.

Liver.—Pale, fatty, 40½. oz.

A few small gall-stones in bladder.

Kidneys.—Each 4 oz. Cortex a little diminished. Capsule peeled fairly easily, leaving a somewhat roughened surface.

Joints.—Left great toe: Cartilage eroded. Cancellous tissue exposed. No urate deposit. Left knee similar changes. No urates. Metacarpo-phalangeal joint of right index finger in same condition as great toe.

Here we have extensive rheumatoid changes affecting the same joints in the same way as in the previous cases where urates were found, but there are no urates. Kidneys slight fibrous changes. Heart not markedly hypertrophied. Death from pneumonia.

These three interesting cases were all diagnosed during life as chronic rheumatoid arthritis or progressive chronic articular rheumatism. In two of them urates are found in the joints after death. In the third none.

Now, according to ordinary pathological nomenclature, the first two cases would be called gout and the third rheumatoid arthritis, but during life they were indistinguishable. There is, then, some confusion of ideas between clinical medicine and pathology.

From my point of view the joint changes in all three cases were the work of uric acid, but in one after it had set up the mischief which ended in the more or less complete destruction of joints, it was got into solution and passed in the urine, so that at the *post-mortem* none was left in the joints; in the other cases, no doubt, a good deal of urate had been passed in the urine, and if the patients had lived longer none would have been found in their joints either, and all three cases would have been called rheumatoid, which is absurd.

It will be observed that the case in which there were no urates

differed from the others chiefly in this, that she was much more crippled by her disease. We are told that she had done no work for eight years, and when in the infirmary for the last year or eighteen months of her life her joints were so stiff and fixed that she was practically bedridden.

Now the effect of this helpless condition would be to diminish metabolism. Urea and acidity of urine would steadily fall, the alkalinity of the blood, and therefore its solvent power over uric acid, would increase, and it would become more watery and poor in salts (conditions discussed in the previous chapter) and excess of uric acid would be excreted so long as there was any in the body to be got into solution. The liver and spleen would first be cleared, and then gradually during weeks and months the urates in the joints would also be got into solution and passed out in the urine.

And excessive excretion of uric acid was no doubt occurring in the other cases also, as metabolism was probably low in all; but in these cases the plus excretion had been less marked or less prolonged, and some urate remained undissolved at the time of death.

It will be seen that Case I. had well-marked granular kidneys, and yet the specific gravity of the urine was, on some occasions, as high as 1018 or 1020. I have no doubt that on these occasions he was excreting an excess of uric acid, which raised the specific gravity of his urine in spite of his having granular kidneys and low urea.

I will now mention a case I was fortunate enough to see in the *post-mortem* room at St. Bartholomew's. It was that of a man aged 41, who had extensive joint-troubles with granular kidneys, endo- and pericarditis. Of his joints, some had urate and others none; thus there were rheumatoid changes in both knees and both elbows, the right ankle, and the right great toe, and there were urates in both elbows, the left knee, and the right great toe. Sir Dyce Duckworth, who was looking at the *post-mortem*, said that seen apart these joints might be called gouty and those rheumatoid.

This man also had granular kidneys, and, if I may trust my memory, this had not been diagnosed during life because the specific gravity of the urine was too high; doubtless this was due to an excessive excretion of urates, which would have been found if the urine had been examined. The blood also would have shown numerous granules.

The amount of urate was probably from the action of various causes, not exactly the same in any of the joints to start with, and when the increased alkalinity and watery condition of the blood began to act and remove urate equally from all, the result was that some were cleared before others, for if equals be taken from unequals, the remainders are unequal; hence some joints contained a little urate, others none.

"According to Trousseau and Remak, in women the disease [rheumatoid arthritis] is often preceded by megrim," *i.e.*, by paroxysmal excess of uric acid in the blood (Latham, *Lancet*, 1901, vol. i., p. 999), a very interesting record, as others have pointed out a similar relation between rheumatic fever and migraine.

We now see that the "intimate relationship of rheumatism and gout" is not a supposition but a fact, and a fact founded upon community of causation; that some very simple facts with regard to the solubility of uric acid will enable us to explain the phenomena and symptoms of both diseases; and, lastly, that the failure to find urates in the joints after death is no proof that they have not been there and produced the lesions of cartilage and fibrous structures which are found.

With regard to the causation of joint changes it is interesting to note that M. Potain says (*Sem. Méd.*, December 18, 1896), that the deformity in arthritis is due to loss of muscle power, which again is due to atrophy of muscle, and that similar changes are found in traumatic arthritis.

We now know the causes that affect the solubility of uric acid in the blood and their mode of action; we know also something of its relation to the joints, fibrous tissues, and organs of the body; we know that a large number of drugs which interfere with the solubility of uric acid in the blood precipitate more or less irritation of fibrous tissues and joints, and probably hundreds and thousands of relapses, both of arthritis and endocarditis, have been produced by administration of ammonium salts alone; indeed, I believe the use of these salts for bronchitis in the young has often produced an arthritis or endocarditis in addition to the original trouble. We also know that everything which we formerly used empirically in the treatment of acute rheumatism—alkalies, colchicum, hot baths and blankets and salicylates—have this one effect common to them all, that they increase the solubility of uric acid in the blood.

While we believe that rheumatism is due to some unknown cause, miasm or microbe, we shall continue to say that the patient had an attack or relapse with endocarditis, which resulted in serious

heart lesion and a crippled life, and shall regard these things as inevitable, much as do the jury who bring in a verdict of "death by the visitation of God."

But once we realise that these diseases depend upon the quantity and solubility of uric acid in the blood, and that the quantity of uric acid in the blood and its solubility in that fluid are completely within our control, we shall pass at one bound from the unknown to the well known, shall see that these deadly diseases are not the result of unpreventable causes, but of our own dietetic follies, and that our children need not be crippled or decimated by them, if we allow them to live according to their own inclinations on milk, breadstuffs and alkaline vegetables, and abstain from forcing down unwilling throats the stimulating but deadly products of animal metabolism and the equally poisonous and stimulating vegetable alkaloids.

For some years past I have been in the habit of asking all rheumatic children I have seen this question: If I offered you a plate of fruit and a plate of meat, which would you take? I have never seen a child who would have taken the meat.

I have already referred to the cases of Sir W. Foster, who, with the object of diminishing the amount of sugar, administered lactic acid to two patients suffering from diabetes, with the result of producing severe arthritis resembling acute rheumatism, and in one of the cases six attacks were produced by repeated administration of acid.

I believe that any acid that is absorbed and affects the alkalinity of the blood will produce similar effects if it is given when there is an excess of uric acid in the blood; and the point about diabetic cases is that they generally have an excess of uric acid in their blood and the defective capillary reflux and high blood pressure it produces, as pointed out in chapter xiv.; and not only acids, but any drug (and there are many of them) that interferes with the solubility of uric acid in the blood will do the same thing.

Sir T. Lauder Brunton speaks* of cases in which both rheumatism and endocarditis have been produced by injecting acids into the blood, and he also mentions an instance in which drinking the red wine of Southern Europe appeared to keep up a lumbago from which he was suffering, and that it had often acted similarly in other cases. With regard to endocarditis, he refers to a thesis for the degree of M.D. in the University of Edinburgh, presented by

* *Proceedings of the Royal Medical and Chirurgical Society*, April, 1890.

Dr. J. A. MacDougall in 1865, and says that he was able, by injecting phosphoric acid into the blood, "to produce undoubted evidence of endocarditis."

Coming a few years after these remarks of Sir T. Lauder Brunton's were made, the following case startled me greatly, and made me fear that I had inadvertently caused both rheumatism and endocarditis.

M. J., aged 30, was suffering from phthisis of the left lung. In March, 1894, he had some fresh signs of consolidation at the left base, with a temperature of 102° F. After a few days in bed the temperature began to come slowly down, and on March 9, as his appetite was bad and he was a good deal pulled down by night sweats, I gave a mixture containing some nitro-hydrochloric acid and a few minims of liq. strychninæ. On March 10 he complained of pain and tenderness about the left shoulder-joint, increased by movement of the limb; the temperature had risen very decidedly, and on listening over the apex of the heart I found a distinct systolic murmur which was not present before. I at once stopped the mixture and gave salicylate of soda in its place, and on March 11 the temperature was lower and the pain in the shoulder had gone; but the murmur remained, and though I saw him from time to time for six months after this, it never completely disappeared. I have no doubt that I thus caused some arthritis, and, I fear, some endocarditis as well.

Since this I have several times seen an arthritis of a neighbouring joint (the shoulder) supervene on a gout of the respiratory fibrous tissues, such as is described in fig. 74, and others have recorded similar experiences, as shown in chapter ix.; and such a metastasis is often a good sign, for as the arthritis gets worse the irritation of the more important respiratory tissues will diminish.

J. B., aged 7, suffering from chorea, was admitted into the Royal Waterloo Hospital, October 29, 1894. Temperature on admission 99·6° F., pulse 80 to 90. I examined the heart, and, finding no murmurs, put her on a mixture containing ♏xv. of liq. arsenicalis, to be taken three times a day. On October 30 the temperature was nearly normal, on October 31 it rose to 100° F. in the evening, on November 1 to 100·6° F., and on November 2 to 100·4° F. in the evening. It then kept between 99° F. and 100° F., but on November 6 the pulse had risen to 140 and above, and it remained quick for some time. The arsenic was left off. On November 7 the highest temperature was 99·8° F., and liquor arsenicalis ♏iii. was given three times a day. On November 8 the

highest temperature was 99·8° F., on November 9, 98·8° F. From this the temperature remained just about 99° F. until November 21, when the arsenic was left off altogether. On November 22 a well-marked post-systolic murmur was observed at the apex. From this onward the temperature kept about 99° F., rising to 100° F. on December 14 and 100·6° on December 18. By this time the chorea, which had improved markedly on the large dose of arsenic given at first and more slowly afterwards, was gone. She was allowed to get up, and on December 27 she went home, the murmur at the apex remaining well marked to the last.

I should say that Dr. Huntley, our very able resident medical officer, believed that there was a slight systolic murmur at the apex from the first; but that it became more marked while under observation. It is certain, however, that I heard no murmur on admission, for my rule is not to give arsenic, and certainly not the large dose I gave in this case, if there is any sign of endocarditis (see remarks on the causation of chorea, further on).

The fairly marked rise of temperature under the arsenic, and its fall later when it was reduced and left off, point to some inflammatory trouble in the body, and there was no evidence of any except in the heart; then the marked rise in the pulse rate about November 6 may be taken as pointing to some fresh heart trouble.

A. S., aged 7, was admitted into the Metropolitan Hospital on February 12, 1895, suffering from broncho-pneumonia, coming on pretty suddenly, with headache and shivering. The temperature on admission was 104° F., but it at once began to slope downwards, touching normal on the evening of February 16. On February 17 it rose slightly above 100° F. in the afternoon and evening, but from that up to February 20 it kept between normal and 100° F. On admission dyspnœa was the most obvious sign, and percussion was altered over several portions of the left lung, but a few days later there were more obvious signs of consolidation at both bases (was this a gouty or rheumatic inflammation of the respiratory fibrous tissues causing broncho-pneumonia? and was the subsequent endocarditis a mere spreading of this trouble? See chapter ix.). There was no murmur over the heart and no increase of dulness. On February 20, after the temperature had been at 100° F. or below it for four days, a systolic murmur was noticed at the apex of the heart, and the cardiac dulness was also found to be a little increased to the right. The temperature now continued for some time between 98° F. and 100° F.; on February 28 it became subnormal, making, however, daily excursions from 96° F. to 98° F. On March 6 it

became more steady and kept nearer the normal, but occasionally ran up to 100° F. On March 9 the systolic murmur was still heard at the apex, and reduplication of the second sound at the left base. On March 13 I gave, three times a day, a mixture containing tincture of digitalis ℥iiss, dilute sulphuric acid ℥v., and some glycerine. I gave this because I was not very certain whether the slightly raised temperature and the apex murmur meant endocarditis or not; and, on the other hand, if the murmur was merely due to dilatation, the digitalis might be of some use. As there was some doubt, however, I told the house physician to stop the drugs at once if the temperature rose. Fig. 69 shows the effects produced, and in it we see that on March 12 the temperature ran from normal in the morning to 98·8° F. in the evening,

On the 13th the mist. digitalis acida was given, and the evening

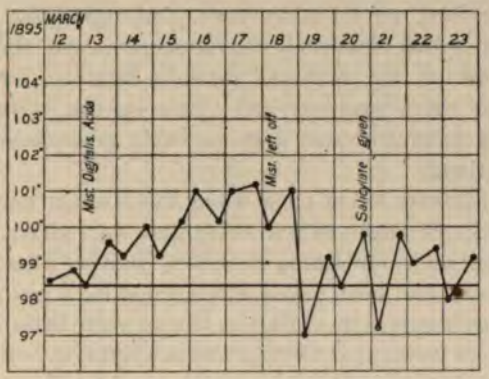

FIG. 69.—TEMPERATURE CHART OF RHEUMATIC ENDOCARDITIS SHOWING THE CAUSE AND CURE.

temperature rose to 99·6° F., on the 14th to 100° F., and on the 15th to 100·2° F., and on the 16th and 17th it touched 101° F. three times, and was never below 100° F.

On the 18th the mixture was left off, and though the temperature again rose to 101° F. that night, it was only 97° F. next morning, and during the following days never quite reached 100° F. The cause being removed the effect began to diminish and disappear; but to aid and quicken its disappearance some salicylate was given on the 20th, and on the 22nd and 23rd the temperature began a further steady fall.

If there had been any arthritis I should have said the temperature was due to that, for it rose on the administration of drugs

which would have made arthritis worse, it fell when these drugs were left off, and went down still further when salicylates were given. There was, however, no sign of arthritis, but there were signs of its nearest relation—endocarditis. The systolic murmur remains and is now more distinct than before, and can be heard outwards in the axilla. The rest of the history is uneventful; the temperature during April and up to his discharge on May 8 kept between 98° F. and 100° F. The systolic murmur continued, and on April 3 the whole of the first sound was replaced by a murmur.

I have little doubt, that we had here to deal with an endocarditis, originating, as I have suggested, in the great strain, which falling temperature and its consequent rising blood pressure put upon the valves of the left side of the heart (post-febrile collæmia about February 16 and 17), or as part of an inflammation of fibrous tissues which was due to urates from the first; that this went smouldering on for some time, accounting for the irregular temperature which followed convalescence, and then blazed up again at once on the acid and digitalis mixture, for the digitalis not only put extra pressure and strain on the valves of the left side, but the sulphuric acid very probably precipitated some fresh urate upon them.

The temperature fell at once when these drugs were left off, and became still more steady when salicylates were given, but the local irritation went on smouldering as before, though before he went out his temperature had been practically normal for a few days.

This chronic irritation of fibrous tissues with little or no fever (I may remark in passing) is exactly the condition in which salicylates will not completely cure, but in which a uric-acid-free diet may be expected in the course of a few months to completely extinguish the smouldering disease, a disease which under ordinary diet is practically certain to go on for years with slowly increasing lesions till death ends the scene. Indeed, it must be evident that while urates and xanthins are being constantly poured in day after day in the food, neither salicylates nor anything else can keep the tissues completely clear of them.

If anyone were to say to me this was rheumatic endocarditis due to a microbe, I should only require to ask him one question, viz.: How, then, did the digitalis and sulphuric acid affect the microbe and cause the rise of temperature? or how was it that the ammonia of the older experimenters did not overcome the microbe, while their potash and soda did? The answer to the one question is the answer to the other; all the drugs mentioned acted on the solu-

bility of uric acid, and the microbe, if present, was of no consequence except as a possible precipitating agent.

For comparison with fig. 69 I will now give fig. 70, the temperature chart of a patient, Amelia M. J., aged 21, admitted into the Royal Waterloo Hospital in March, 1897.

Her history showed that she had diphtheria badly in 1895 and rheumatic fever in November, 1896, being seriously ill and in bad health ever since.

Examination of her chest showed obvious hypertrophy and dilatation of the heart, with well-marked evidence of mitral disease and some doubtful evidence of trouble at the aortic orifice also.

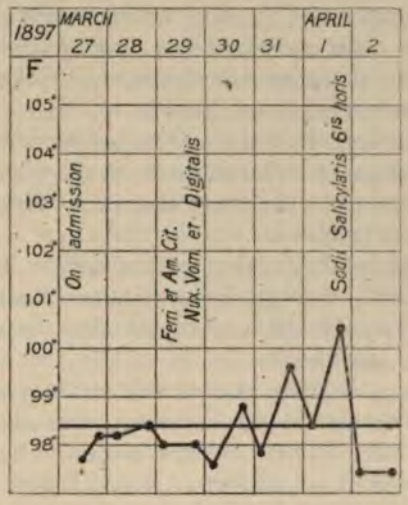

FIG. 70.—TEMPERATURE CHART OF RHEUMATIC ENDOCARDITIS, ANOTHER CASE.

Her temperature on admission was 97·6° F. and her pulse 114, decidedly irregular both in time and force.

As the temperature remained subnormal on the day of admission and on the following day, I ventured, on March 29, to give her some nux vomica and digitalis, for which there were all the usual indications, these being added to the mist. ferri et am. cit. of the hospital.

We had, then, in this mixture three drugs which would tend to retain uric acid in the tissues and make arthritis worse, namely, the iron, the ammonium and the nux vomica; and the digitalis would probably raise the blood pressure and put some little extra strain and tension on the valve structures of the left side.

There was no previous sign of endocarditis, for the temperature was subnormal and the pulse was quick, and gave all signs of heart failure; and though the rheumatic history was recent, the fires of inflammation seemed to have quite died out.

It was, therefore, a surprise to me to find that on the evening of March 30 the temperature rose to 98·8° F. and on the evening of the 31st to 99·6° F. Accordingly, on April 1 I stopped the mist. of March 29 and gave salicylate every six hours.

The temperature rose that evening to 100·4° F., as the salicylate had not had time to come into action, but fell next morning to 97·4° F., and never rose again above normal.

I have here, again, no doubt that the drugs given relighted a smouldering rheumatism of the heart valves, an endocarditis which, owing to the serious valve lesions and the depression produced by very defective circulation, had previously given but little sign in the temperature chart.

These figures seem to speak for themselves and demonstrate the causation of a relapse of endocarditis by drugs which clear the blood of uric acid at the same time that they put pressure and strain on the fibrous tissues involved.

And I should take this view of the matter even if I did not already know that I can produce a relapse of arthritis in anyone who has previously suffered from it with these drugs or with others which act in the same way.

While speaking of these cases I will mention the suggestion of my friend, Dr. Theodore Fisher, in a most interesting article (*Lancet*, 1896, vol. ii., p. 170), that Dr. Caton's treatment, by rest and iodides, with salicylates and local blisters, of which I shall speak further on, cures such cases, because forty days rest in bed allows dilated hearts to recover themselves.

In the case of which the temperature is given in fig. 69 rest in bed for nearly three weeks produced no obvious effect on the heart's condition and the administration of drugs that would probably have done good for a dilated heart, but which would have caused arthritis in anyone who had previously suffered, at once sent the temperature up and probably aggravated the heart lesion.

Where there is difficulty in the diagnosis between dilated heart and endocarditis, perhaps standing, as in the case of A. S., entirely alone and apart from any arthritis, I suggest that some of the drugs used in these two cases (figs. 69 and 70) should be given, for if we have to deal with a dilated heart its condition should improve under this treatment and the temperature should remain steady; while if

there is recent smouldering endocarditis, the temperature will at once run up as in these figures, and its careful treatment with salicylates followed by diet is indicated. I may say also in this connection that I cannot agree with the remark of Jaccoud (*British Medical Journal*, Epitome, November 28, 1896, p. 88) that salicylates are contraindicated in rheumatism with visceral lesions, that is, if these include endocarditis.

I should acknowledge that severe visceral lesions, by upsetting the nutrition and metabolism of the whole body, often produce conditions which are unfavourable to the best action of salicylates, to which I shall have to refer when speaking of fig. 71; but I am decidedly of opinion that in conditions of acute endocarditis, such as we are probably dealing with in figs. 69 and 70, there is no better drug than a salicylate, which, if it cannot be taken by mouth, should be applied to the skin as salicylate of methyl.

In chronic endocarditis without rise of temperature, these drugs, just as in chronic arthritis, are of comparatively little use; and here diet will, I believe, be found to yield more and more frequently, the oftener it is resorted to, the most satisfatory results.

L. G., aged 45, was admitted into the Metropolitan Hospital on January 22, 1891, suffering from gout in the fingers of the right hand. He had gout first in toes and instep in 1882, and since that in the fingers, toes, ankles, or knees. The pain and swelling in the fingers, which were swollen, tense, and shining, began two days before. Temperature on admission 101° F., rose at night to 102° F. He was given a mixture containing gr. xx. of salicylate of sodium four times a day. On January 24, the pain in the fingers had ceased. The temperature fell in the evening to 99·6° F. After this he went on well, and the salicylate was left off on February 7. On February 9 and 10 he suffered from pain due to an alveolar abscess. On February 11 the temperature rose at night, and there was some return of the gout in the fingers and in the bursa of the olecranon process on the left side. On the morning of February 12 the temperature was 100·4° F.; the teeth stumps were extracted and some salicylate given again, and the temperature soon fell to normal and the pain went.

Note the speedy relief of gout by a salicylate; in my experience it relieves all arthritis due to uric acid, provided that it is fairly acute, which means that the alkalinity of the blood is low.

I have already mentioned the case of a boy where similar teeth trouble brought about a relapse of acute rheumatism; and I have also seen a case where the fever of an attack of pneumonia produced a relapse of gout in a patient who had had previous attacks.

E. S., aged 36, admitted into the Metropolitan Hospital on December 31, 1894, suffering from acute rheumatism; had been confined nine weeks before. The pains began three weeks before admission, first in the head and then in the limbs, shoulders, knees, wrists and elbows in that order. The joints were all very tender. The temperature was 102° F. She was given a mixture containing salicylate of sodium gr. xv. and bicarbonate of potassium gr. x., to be taken at first every two hours. On January 2 the temperature was 100° F., but the joints were still tender. The bicarbonate of potassium was omitted from the mixture. The temperature ran up that night to 102·8° F. (the highest it had been since admission), and there was a sharp return of all the pains. It fell to 100° F. the following morning, soon went down to normal, and never rose again.

Now what was the meaning of this sharp and sudden relapse when the drugs were altered? Was it due to the untamable microbe? I believe it was simply and solely a matter of the solubility of uric acid, for I have observed the same thing before under similar conditions.

Some years ago I had under my care a patient suffering from subacute Bright's disease whom on admission I had put on a mixture containing citrate of potassium. After she had been on this for several days she got some pain and swelling in several joints, so I stopped the potash salt and put her on salicylate of sodium, and in a few days her pains were very much better and the salicylate was therefore left off and the potash mixture resumed; here again, just as in the case of E. S., there was a sharp but temporary return of all the joint pains as the result of the change of drugs.

It seems, then, that when arthritic pains are being relieved by a salicylate, it will make them worse to add potash, and conversely, when arthritic pains are being relieved by potash, it will do harm to add a salicylate. My own personal experience quite bears this out, for when some years ago I had my uric acid under less perfect and complete control than at present, I used occasionally after severe exercise in hot weather to get some pain and stiffness in the fascia either of the neck or the lumbar region; and I often found that these troubles were completely removed by a few doses of salicylate of sodium, so long as I kept quiet and cool in the house in the morning; but if in the afternoon I went out and got overheated, still continuing the salicylate, my pains returned, and were worse—perhaps much worse—than if I had taken nothing.

Now what is the effect of going out and getting hot? It has

been shown by Sir A. Garrod and myself that it produces a fall in the hourly excretion of acid in the urine; say the hourly excretion of acid in any individual is equal to 3 gr. of oxalic acid, then going out and getting very hot will, other things being equal, reduce it to 1½ gr. or 2 gr. in the following hours; that is to say, getting hot is equivalent to a dose of alkali.

But we have already seen that alkalies and salicylates do not

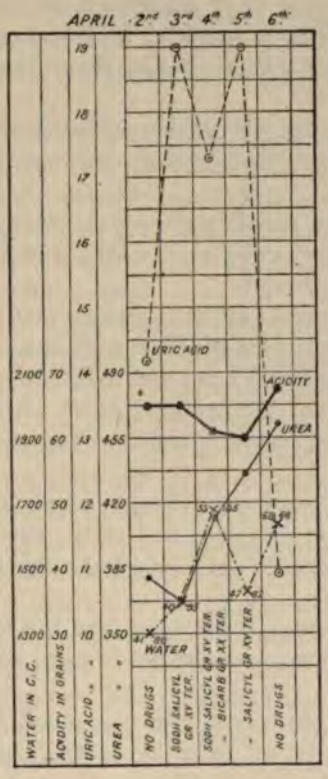

FIG. 71.—EFFECTS ON EXCRETION OF URIC ACID OF GIVING BICARBONATE OF SODIUM WITH SALICYLATE OF SODIUM.

pull well together, and we know that uric acid may be excreted in excess under alkali or under salicylate, and it must be extremely annoying to preconceived opinions that giving the two together does not produce the best effect of all; but unfortunately it does not, as can be proved by experiment.

Fig. 71 shows the effect of taking in physiological conditions a

mixture of salicylate and bicarbonate of sodium, and before proceeding to describe it I must point out that in all ordinary curves of excretion under salicylates, the drugs being continued day after day in the same dose, the excretion of uric acid rises to its highest point on the first or second day that the drug is taken, and after that, however long the drug may be continued, it will never again rise to the same height (see fig. 8).

But in fig. 71 we see that the excretion of uric acid under salicylate of sodium rose to 19 gr. on April 9, fell to 17¼ gr. on the 4th, and rose again to 19 gr. on the 5th; we have here, then, an excretion which is quite different from that of the ordinary excretion of uric acid under salicylates.

On April 2 no drugs were taken, acidity stood at 65 gr. of oxalic acid, and uric acid exceeded its usual relation to urea in formation by some 3 gr.

On April 3, 15 gr. of salicylate of soda were taken three times a day; acidity remained at 65 gr. of oxalic acid and uric acid rose to 19 gr., or 8½ gr. above urea.

On the 4th the same dose of salicylate was taken and gr. xx. of bicarbonate of sodium were added to each dose.

Acidity fell to 61 gr. and uric acid fell to 17¼ gr.

This might be but the ordinary curve of excretion under salicylate, in which case uric acid might be expected to fall still further on the 5th.

On the 5th the same dose of salicylate is taken, but the bicarbonate of sodium is left out, and with this uric acid does not fall; on the contrary it rises to 19 gr., the same height as on the 3rd.

On the 6th no drugs were taken, and the natural result is that uric acid falls down considerably below urea, which has been rising for some days.

It seems to me, then, that there was something on April 4 which interfered with the normal excretion of uric acid under salicylates, and that the bicarbonate of sodium and the fall of acidity it produced, in spite of a rise of urea, were the cause of this, and that if from the 3rd to the 5th salicylate alone had been taken we should have had on the 4th a rise to 20 gr. or 21 gr., and on the 5th a marked fall to 15 gr. or 16 gr.; but as it was, the amount of urate held back on the 4th enabled the excretion to rise to 19 gr. again on the 5th.

I conclude that the mixture of salicylate and bicarbonate of sodium is unfavourable to the solution of uric acid, and produces less excretion than the same dose of salicylate given alone.

I have previously referred to the chemical composition of salicyluric acid and to what is known about its solubility, and have suggested that this might be found to explain the result, but clinically the facts are of far more importance to us than their chemical explanation.

Now it is well known that salicylic acid compounds act best in acute arthritis, and better the more acute the case and the higher the temperature; and it is a matter of the most simple observation that the higher the temperature the higher the acidity of the urine, the greater the hourly excretion of acid, and the less the alkalinity of the blood; therefore salicylates act well when the alkalinity of the blood is low.

It is further known that in subacute cases with but little rise of temperature salicylates act less satisfactorily, and I have pointed out that in such cases their activity may be increased by giving them along with substances which raise the acidity or in alternate doses with an acid; therefore salicylates act badly when the alkalinity of the blood is high or undiminished.

It appears, then, that uric acid in the blood may be in solution either with a salicylate or with an alkali (potash or soda), but it cannot be in solution with both at one and the same time; and that if it is in solution with an alkali and a salicylate is added this will diminish the alkalinity and hinder the solubility of uric acid under an alkali; but until the alkalinity has been very greatly reduced the uric acid will not pass into solution as salicyluric acid, that is to say, between the two drugs there is a dead point at which the uric acid is not in combination with either, but is rendered insoluble, and driven out of the blood into the fibrous tissues of the joints or fascia, producing a relapse of the gout or rheumatism and a rise of temperature. If the salicylate is continued the alkalinity falls still further, and then salicyluric acid is formed and got into solution; the uric acid passes freely in this form from the joints into the blood, the temperature falls, and the pains subside once more (see also uric acid filter experiments, chapter v.).

Now, what occurred in the case of E. S. was that she was being given a considerable amount of potash along with some salicylate and her urates were got into solution with potash and little or not at all with salicylate; but when the potash was left off the alkalinity fell, the potash lost its hold over the urates before the salicylate gained it, and the urates were for a time driven out of solution into the joints and fibrous tissues, producing a sudden relapse of all her pains and a temperature of 102·8° F.; later on, the salicylates had it

all their own way, and there was no further joint irritation or rise of temperature. This shows that salicylates control the pain and temperature of arthritis simply by eliminating uric acid; if anything prevents their eliminating uric acid the pains promptly return, and the temperature rises in spite of them.

I have been told a fact of great interest in this connection by Dr. W. Goodson, of Stratford, E., namely, that his stock mixture of salicylate always used to contain bicarbonate of potash, but one day the potash salt ran short and acetate of ammonium was put in its place, and this has been continued ever since, as it was soon found that the effects of the mixture in curing rheumatism were greatly increased. A little later Dr. Goodson came on this book and there saw the probable explanation of what he had observed.

I may also mention that I have been told of a practitioner in India who refuses to consider as rheumatism much of the arthritis he sees there, because salicylates do not relieve it; but this, if I am right, is exactly what I should expect, for salicylates will not relieve rheumatism even in this country when the weather is very hot and causes much perspiration, and Professor Latham has remarked (*Medical Magazine*, March, 1895) that salicylates act best when the patients are kept cool (see also article by the author on "Gout and Rheumatism" in the *Medical Annual*, 1897). And Dr. Drummond of Talawakelle, Ceylon, writes to me: "I find salicylate of soda out here in the tropics *not* so good as you find it at home."

The fact that salicylates fail to relieve arthritis in a hot climate is no proof that the arthritis in question is not rheumatism or not due to uric acid, but merely shows that the practitioner who would draw such a conclusion is ignorant of the *modus operandi* of salicylates, and the chemistry and physiology that condition it.

To feel joints and tissues becoming painful and stiff as the external temperature rises when salicylates are in circulation, and the same tissues becoming supple and painless as they are exposed to a cold wind or otherwise uncovered, is a revelation in the pathology of rheumatism to these who have experienced it.

Not only are those on salicylates immune to the evil effects of cold, such as arthritis, myalgia, or catarrh, but cold actually does good, and heat, far from doing good, does marked harm.

I have looked in vain for any explanation of these facts and their possible relation to microbic action in the writings of other observers, and I believe that the only explanation lies in the effects of acids and alkalies, and so of heat and cold, on the solubility of the compound which glycocine forms with salicylates (see fig. 8).

My opinion was also asked by Dr. Osburn Cowen, of Thornton, Eaglehawk, Victoria, as to the causation of an arthritis in a case which he published in the *Inter-Colonial Medical Journal*, March 20, 1900, p. 160, under the heading "Case of Puerperal Infection, presenting some unusual features."

On p. 165 the record is as follows: Patient aged 29 years, primipara. On the twenty-sixth day of illness "complains of pains in knuckles. 9.45 p.m.: Temperature 104·7° F., the highest during the illness; pulse 140. Ordered salicylate mixture and hot pack and she perspired profusely and slept well.

"Thence ensued what Dr. Peebles, who saw her with me next day, agreed was a genuine polyarthritis rheumatica, affecting practically every joint in the body, including even the vertebral and maxillary articulations."

The further history shows that there was no suppuration in any joint, that resolution was rapid, and temperature fell to normal in five days in spite of an invasion of the endocardium and the production of a mitral murmur.

Now, there can be no difficulty in reading the full sequence of causation in this case after what I have just been saying, and I gave it as my opinion that it was without doubt a polyarthritis rheumatica, due to the occurrence of the dead point between salicylates and alkalies.

The alkali was provided by the hot pack and profuse perspiration, the salicylate was given in a mixture.

On the morning of the twenty-seventh day the urates in the blood were not in solution with alkali because the salicylate prevented that, they were not in solution with salicylate because alkali prevented that; they were therefore not in solution at all, but were driven violently out of the blood into all the fibrous tissues of the body, and the acute general arthritis and endocarditis were the results of this.

Later one of the combatants got the best of it, either the salicylate or the alkali, and then the uric acid was eliminated in the urine and all went well.

If the blood had been examined on the morning of the twenty-seventh day few or no granules would have been found; later during resolution they would again have become numerous.

And this relative absence of uric acid from the blood can be produced even in physiology by administering a small dose of salicylate during the morning alkaline tide, or at other times in the day by administering salicylates and alkalies together, and if this

is done when there are considerable quantities of uric acid in the blood, more or less arthritis will be produced, as in the cases I have previously mentioned, and in my own case in reference to fig. 74.

But anyone can produce these results more or less markedly according to the amount of urate available in the circulation, together with a corresponding fluctuation in the number of blood granules to be seen under the microscope, and salicylate of soda with hot pack is an almost infallible prescription for more or less arthritis.

Now, this to my mind carries with it the entire etiology and pathology of acute rheumatism, and proves that it is absolutely dependent on the solubility of uric acid in the blood, and that microbes have at most but a temporary and quite secondary influence, in that they may produce fever and rise of acidity, which is one of the conditions unfavourable to the solubility of uric acid, except when salicylates are in circulation; and this very important exception furnishes the master-key of causation.

On the other hand, I have seen salicylates given in various local and traumatic inflammations and in pyæmia, and their effect on the pain and temperature was just nothing, because these were not due to uric acid. Further, I have pointed out* that the compounds of salicin and salicylic acid are powerful in the relief of acute rheumatism exactly in proportion to their power over the solubility and excretion of uric acid; and that those that have least power of elimination (such as salicin) must be given in much larger doses than those (such as salicylic acid) that have most. Then aspirin and novaspirin are more powerful than salicylic acid, because they are compounded with an acid radical which aids solution (see "The Salicylates in Diagnosis and Treatment," *Medical Record*, New York, December, 1907). I make bold to say that every drug that has ever been used with benefit in acute rheumatism in the past and every drug still to be discovered that may be used with benefit in the future, will be found to do good in direct proportion to its power of eliminating uric acid in the urine.

For a series of cases of rheumatic fever where salicylates were given quite wrongly in combination with local warmth, fomentations and poultices, where they, of course, failed to do good and were unjustly blamed for the failure, and where, most surprising of all, surgery was resorted to to effect a cure, see *Lancet*, 1903, vol. i., p. 228, and for my protest against the unjust blame of these useful drugs see letter to the *Lancet*, 1903, vol. i., p. 398. These cases

* *Medico-Chirurgical Transactions*, vol. lxxiii., p. 297.

merely show what we have already demonstrated above, that salicylates with heat or alkalies do harm in arthritis due to uric acid. The surgeon who published them makes the interesting and by no means improbable suggestion that endocarditis also got worse under his treatment. He said that it was the delay of surgical treatment that "ruined" his patient's heart. I consider that it was the absolutely wrong use of a powerful drug which produced this result. As I point out in my letter, salicylates properly given can cure acute uratic arthritis in thirty-six hours easily; if not properly given they may kill by producing severe arthritis and endocarditis. This is the most important point in the use of salicylates, the point which gives both the correct etiology of the disease (proving it to be due to uric acid) and the explanation of numberless failures in practice. And this must be my excuse for the space I devote to the subject here, and for its frequent mention in this volume.

I hear of similar misuse of these powerful drugs in many directions and of cases of arthritis, which could be cured easily in two days, requiring in consequence ten to fourteen days of treatment.

I shall now shortly mention one or two cases in which a relapse of chronic rheumatism was produced by drugs which cause precipitation of urates.

T. P., aged 71, was admitted into the Metropolitan Hospital on January 14, 1895, suffering from chronic rheumatism (? gout). He had had an attack of sciatica ten years earlier, and two years later arthritis in both hands. This he had had off and on ever since, chiefly in the legs, but the hands were a good deal distorted and crippled. He was ordered salicylate of sodium and given some cod-liver oil. He improved steadily, and was soon able to walk much better, and had little or no pain. The temperature varied from 97° F. to 99° F. On February 5 he had some little bronchitis, the salicylate was stopped, and he was given a mixture containing ammonia and senega. As the pain returned the ammonia mixture was stopped and the salicylate resumed on February 9. On February 13 the pains were distinctly better, but the salicylate was kept on, and, as the previous dose was small, it was increased to gr. xv., and the improvement was steady and continuous. We have here only the patient's word for it, as the temperature showed nothing, but there was no reason why he should have complained of more pain just at the time the drugs were altered.

H. K., aged 66. This case, very similar to the above, was suffer-

ing from chronic rheumatism and sciatica. He was admitted into the Metropolitan Hospital on January 15, 1895. There was a history of having suffered for nine years. Pains were now chiefly in left knee and hip. He also was put on salicylate and improved considerably. On February 23 the note says: "Can get about better, and pain is, comparatively speaking, gone." On March 20 he got some bronchitis. The salicylate was stopped, and mist. senegæ cum ammonia ordered. On March 26 the pains were decidedly worse again, especially in the knee. He was ordered to have the salicylate mixture as well as the ammonia, and the pains soon got better.

I have already said that urate of ammonium is one of the more insoluble urates, and that ammonium raises the acidity of the urine and increases the hourly excretion of acid. It would therefore increase gouty or rheumatic pains when given alone, but would not interfere with the action of salicylates; on the contrary would aid it (see p. 171 and elsewhere).

I could easily give a number of similar cases; indeed, a week never passes without my seeing one or more of them. Almost every time a uric acid headache is cured some joint pains are produced, and in gouty and rheumatic cases the well-known effects of changes of weather can almost always be translated into change in the alkalinity of the blood, secondary to the effects of the weather on the excretion of the skin.

Thus a patient gives me the following history of an attack of gout: He lives in India but occasionally comes to England, and after a previous visit to England, where he had been "feeding up," he felt the heat very much in the Red Sea on the way out, and then in Bombay was exposed to comparatively cold March winds and had a violent attack of gout. Can anything be more simply and easily explained than this history? We have (1) the ingestion of a quantity of uric acid, (2) its solution in the blood (uric acid collæmia) as the result of heat, and (3) its precipitation in the joints by the rising acidity produced by cold winds.*

Similarly in patients who suffer from mental depression, pains in the joints are often looked upon as the harbingers of better things; and in women, when menstruation with its depressing influences causes a rise in the alkalinity of the blood and an excess of uric acid in that and the urine, mental depression or headache are generally worse, while rheumatic pains are to some extent relieved (figs. 31 and 32).

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* See *British Medical Journal*, 1895, vol. i., p. 640.

The effect of change of weather is largely dependent on change of temperature, and this regulates the loss of acids in the form of perspiration, and so determines the alkalinity of the blood and the acidity of the urine. Thus exercise with perspiration (see chapter viii.) lowers the acidity of the urine, increases the alkalinity of the blood and floods it with uric acid.

It follows that heat in any other form, as air baths, water, Turkish baths, or hot applications of any kind, provided they affect a sufficiently large surface, will similarly influence the alkalinity of the blood, the acidity of urine and excretion of uric acid.

Now fig. 72 shows the effect of a Turkish bath on the acidity of the urine, and I give it because it has an important bearing on the causation and treatment of rheumatism.

The upper curve marked N is a reproduction of the curve of urinary acidity in fig. 3, while B shows the effect of the bath on the excretion of acid in the same hours.

At 5 p.m. B was slightly above N, and at 6 p.m. below it, and the net result of these two hours before the bath is that B is lower than N by about $\frac{2}{8}$ to $\frac{3}{8}$ gr. per hour.

In the hour ending 7 p.m. the Turkish bath was begun and ended in the hour ending 8 p.m. Supper was finished in the hour ending 9 p.m., this being exactly the same hour as in fig. 3.

We see, then, that from the time of the bath, 7 p.m., up to 10 p.m., there is a steady divergence of the two curves, N rising while B falls, so that at 10 p.m. B is $1\frac{1}{4}$ gr. below N.

At 11 p.m., however, they come much nearer, but this was due to a rise of B while N remained unaltered. At 5 a.m. they are the same distance apart as at 11 p.m., but at 7 a.m. they are again very close.

In the hours 7 p.m. to 11 p.m. inclusive, N exceeds B by almost exactly 3 gr., if we make no allowance for the fact that B was a little below N to begin with; if we allow $\frac{2}{8}$ gr. per hour for this the effect of the Turkish bath was to diminish the excretion of acid in the urine by 2 gr. in those hours.

This fall in excretion of acid, small though it seems, indicated a very distinct effect on the alkalinity of the blood and the excretion of uric acid, for when the rise of B occurred in the hour ending 11 p.m., there were marked myalgic and rheumatic pains in several parts of the body, which doubtless showed that during the previous hours there had been some excess of uric acid in the blood, and that the fall of alkalinity was now causing its retention in the fibrous tissues.

Practically, the bath depressed the acidity of the urine for twelve hours, the greatest effect being shown in the two subsequent hours, and no doubt a similar bath repeated daily for a week would have a distinct effect on the alkalinity of the blood and the excretion of uric acid, and would thus probably distinctly affect any arthritis due to uric acid.

The first effect would be to increase the excretion of uric acid and relieve the pains of arthritis; but later on, when the alkalinity of the blood began to fall, as at 11 p.m., some urate would again be driven into the joints and the pains increased, this increase of pains being very marked if a patient, after a bath, unwisely exposed

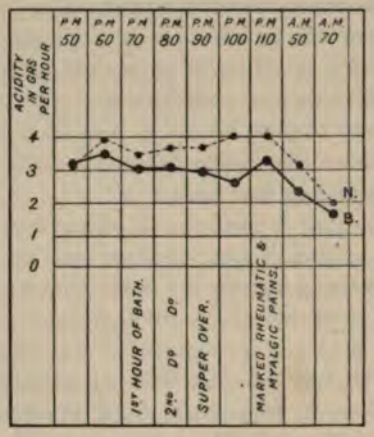

FIG. 72.—EFFECTS OF A TURKISH BATH ON THE ACIDITY OF THE URINE FROM HOUR TO HOUR.

himself to cold and damp, thus checking perspiration, or drank acid wines, which would also diminish the alkalinity of the blood.

The case of J. B., mentioned above, in which the treatment of chorea by large doses of arsenic seemed to produce or increase an endocarditis, raises the question of the causation of chorea, for unless there was some excess of uric acid in the blood along with the chorea, the arsenic would not have produced an endocarditis; and this suggests the further question, Does arsenic cure chorea by clearing the blood of uric acid, or is chorea one of the effects of excess of uric acid in the blood?

There are a few facts in this connection which must be borne in mind, though they do not justify a definite conclusion.

First, then, chorea has a fairly definite relation to acute rheu-

matism, and this seems to be that it precedes or follows it, but does not often accompany it.

Now migraine bears the same relation to rheumatic fever as we have seen above, and migraine is due to collæmia.

Again, chorea, like migraine, coincides with conditions of dyspepsia and debility, in which there is certain to be an excess of uric acid in the blood.

Again, the mental conditions in chorea—the dulness, inability for work, and increase of irritability—are also the symptoms of collæmia.

The late Dr. Sturges considered that chorea was an exaggeration of fidgetiness; and is not fidgetiness a sign of collæmia in gouty adults?

Chorea is said by Dr. Dickenson and others to be due to widespread hyperæmia of the nerve centres, and Dr. Handford (*Brain*, 1889, p. 129) pointed out that overwork produces such congestion of centres and tends to make it persistent, and that this is evidenced in adults by trembling of hands, nervous starting, twitching of orbicularis palpebrarum, and fidgetiness; but overwork (fatigue) also produces collæmia.

Again, chorea is not very distantly related to the tremors of the aged and feeble, and I have observed that these tend to be worse in the alkaline tide hours of the day, and gave acids with the object of diminishing them, in some cases with apparent success.

Dr. Handford also mentions a case where chorea began during menstruation following mental depression and hysteria, and in this case embolism and thrombosis of certain vessels were found at the *post-mortem*.

Chorea often follows shock, fright or emotion, and these conditions suffice to depress the metabolism of the body and produce collæmia.

We see in chapter iv. that Graves' disease bears a similar relation to shock or depressing emotion, and this is true to some extent of Bright's disease, diabetes, and all collæmic diseases; while more recent observations show that the capillary reflux is markedly slow in chorea.

And if chorea is the result of hyperæmia, stasis, or thrombosis in certain nerve centres, it is easy to see how the obstruction of capillaries by uric acid may account for this.

As to the drugs which cure chorea, arsenic probably clears the blood of uric acid, and I have suggested that it may produce endocarditis in doing so.

Antipyrin appears to have been used with advantage by some

(*British Medical Journal*, 1894, vol. ii., p. 1227), and it also cures migraine.

Lastly, salicylate of soda may be injurious in chorea and make the movements worse, and though salicylates do no harm in migraine when given at the right moment, they may intensify it if given wrongly, *i.e.*, at a time when there is much gastric upset with debility and depression; they also, as we know, slow the capillary reflux.

Under these conditions they bring excess of uric acid into the blood, and if the blood is strongly alkaline owing to dyspepsia and debility, the uric acid will combine with the alkali and make the migraine worse; therefore I first use mercury in migraine to clear the blood of uric acid and give metabolism an upward trend, and then follow it by salicylates to carry off the uric acid.

I can easily understand, therefore, that salicylates may make chorea worse, for it is so commonly associated with conditions of debility.

In migraine there is no heart failure, the pain being due to high blood pressure, which heart failure renders impossible; but in chorea there are heart failure and low blood pressure, and salicylate increases collæmia and makes heart failure worse.

There are thus numerous connections between chorea and collæmia, and if chorea is due to collæmia we can at once see the explanation of its relation to acute rheumatism, which is similar to that of migraine.

Chorea, therefore, may be but a variation of migraine, the uric acid collæmia and its circulatory disturbances producing more serious and lasting effects on the more unstable nerve centres of the child.

But in addition to the theories just mentioned there is another, due apparently to the late Dr. Kirkes, which ascribes chorea to embolism of the minute vessels of the brain (corpora striata), the emboli taking origin from the previously inflamed valves of the heart.

It seems to me we can explain all the conditions by a slight modification of this theory if we suppose that the embolic particles originate, not in the valves of the heart, but in what I have called a snowstorm of colloid uric acid in the blood, some of the urate particles collecting and forming here and there more or less permanent obstructions in the minute vessels of the brain. Such a condition would help us to explain, not only the occasional morbid appearances found after death, but would more or less completely

account for several points with regard to chorea which remain inexplicable on other theories.

This condition of the blood, which I have called collæmia, is, I believe, the cause of the general obstruction to the circulation and the consequent high blood pressure which uric acid produces (see chapter v.).

The obstruction is partial and temporary only; the colloid particles pass through the capillaries, though slowly and with difficulty, and then, being carried by the veins to the deeper and warmer parts of the body, are, as a rule, redissolved.

But under *slightly altered conditions* several of these snow-flakes may adhere together and form a mass capable of completely obstructing a capillary or set of capillaries, and so alter, for a longer or shorter time, the function and even the structure of the surrounding portions of the brain.

I have suggested that embolism or thrombosis, thus originating in colloid particles of uric acid in the blood stream, may account for the well-known relationship between such troubles and gout (see also my remarks on thrombosis in chapter xii.).

I have also pointed out that the obstructing influence of colloid uric acid in the blood will account for one feature of Raynaud's disease which is otherwise inexplicable, namely, its limitation to surfaces and extremities, *i.e.*, to exposed portions of the body; and the effects of local cold in producing Raynaud's disease, as by washing the hands in cold water, are well known. I have already mentioned, also, the probable relation of collæmia to cold, acids, &c.

And now we recognise one of the altered conditions which may make the difference between temporary and more permanent obstruction of capillaries by collæmia, and it will be found also to give us an explanation of the well-known large preponderance of chorea in girls, which seems to be from two or three to one.

I have already given this same condition in chapter xi. as the cause of the increased frequency of Raynaud's disease in girls, and have suggested that as girls differ from boys chiefly in having the muscular system less well developed, they will have also, probably, less powerful hearts; and this may just make the difference between the slight temporary obstruction of their capillaries by collæmia, which produces cold hands, and the more severe and permanent obstruction, which brings about actual Raynaud's disease. We can see that the washing in cold water will act just as cold in the test tube (chapter v.), by determining or increasing the precipitation of the colloid, and will make the difference between a few flakes of snow and a blinding storm.

Obviously the same explanation will apply to the preponderance of chorea in girls if it is due to collæmic embolism, for a little weakness of the heart muscle may suffice to make the difference between such slight and temporary obstruction of capillaries as causes general high blood-pressure and the more permanent or lasting obstruction which is the possible cause of chorea.

The same fact may also explain the great value of rest in bed, which relieves the heart of much work; while arsenic not only clears the blood of uric acid, but, as is well known in countries where it is eaten, strengthens the heart and the muscles in general.

In a case under my care the blood pressure rose during treatment by rest in bed and arsenic, though the capillary reflux was slow the whole time, showing that the cure was due rather to strengthening the heart than clearing up the collæmia. Francis M., aged 12, admitted into the Metropolitan Hospital, January 5, 1900. A day or two after admission the pulse was 92, slightly irregular, the blood pressure 90—100, and capillary reflux 7.

About two weeks later, when movements were less, capillary reflux was still 7—8, but the blood pressure had risen to 120.

And a week later, when there were no movements at all, capillary reflux was the same as before, but the blood pressure had further risen to 130.

The chorea in this case followed an attack of sore throat, joint pains and catarrh some three weeks before, and I should read the sequence as post-febrile collæmia, heart failure, chorea, followed by recovery of heart and disappearance of the chorea, in spite of the continuance of some collæmia.

I now shortly mention one more recent case of chorea in illustration of this point. Louisa S., aged 15, a tea packer—the history does not show whether there was any relation between her employment and her trouble—admitted into the Metropolitan Hospital, May 26, 1903, suffering from chorea. On May 28 the note shows as follows: Temperature subnormal; pulse from 96 to 124; capillary reflux on chest 7 to 8 half seconds; blood pressure, which was only obtainable some days later (June 2), when the pulse was still 92 and the capillary reflux as before 7 to 8, 100 to 110 mm. of mercury. She was kept quiet by means of chloral, and large doses of arsenic were administered, and on June 9 the note showed that the movements had become slighter, and that the blood pressure had risen to 125 mm. of mercury. On June 11 there was a sudden return of the movements and the blood pressure was found to have fallen again to 100. On June 16 the movements were again less, and the blood

pressure had risen to 115. On June 23 the note shows temperature has risen towards normal and blood pressure was found to be 120. She went on with various slight fluctuations till August 14, when she was quite well, pulse 72, capillary reflux on chest 7 to 8, blood pressure 135 mm. of mercury, has been gaining weight for the last week or two. The capillary reflux was practically the same when she was well as on first admission, the blood pressure was very distinctly higher and the pulse very much slower, the signs of heart failure had passed away and with them the manifestations of chorea.

With reference to this point I note with interest that Sir Dyce Duckworth says in an article published in the *British Medical Journal*, 1906, vol. i., page 1454 : "It is surely worthy of note that in first attacks of rheumatism and in first attacks of chorea there is not seldom to be observed a distinct degree of cardiac dilatation sometimes independent of pyrexia, pericarditis or appreciable endocarditis."

This has interested me very greatly, for if my pathology of chorea is correct this is the essential feature of the attack, *i.e.*, cardiac failure under collæmia. By the time the heart, by the aid of rest and tonics, has recovered itself the chorea is at an end.

And other forms of tremor are to be met with, be it remembered, under very similar conditions of collæmia with cardiac failure.

I have observed similar changes of blood pressure in quite a number of cases of chorea—in all, in fact, that have come under my notice : the blood pressure is low at first, but as the heart condition improves with rest and tonics and the pressure rises to and above normal, the symptoms diminish. I could easily give more cases showing the same thing. I look upon arsenic merely as a cardiac tonic, and other tonics will do quite as well. I now generally use nux and strophanthus in its place.

Such a causation will enable us to understand completely the relationship of chorea to shock and fatigue. Almost every shock, mental or bodily (and they are generally both), suffices, if at all severe, to suspend digestion, to lower the hourly excretion of urea and of acid in the urine, and so to increase to a corresponding extent the alkalinity of the blood ; and thus, especially in children, to flood it with uric acid ; hence shock often suffices to bring on megrim, epilepsy, or mental depression.

Graves' disease, which I have already suggested (chapter v.) may be due to unrelieved high blood pressure, may also originate in a similar mental shock (see Sir W. Broadbent, "The Pulse," p. 90).

The effect of fatigue in producing collæmia in those who have

large stores of uric acid has already been treated of at great length in chapter viii., and its bearing on the collæmic causation of chorea is obvious.

Some interesting suggestions are made by Dr. Churton (*British Medical Journal*, 1896, vol. ii., p. 715) bearing on these points, one of which is that chorea may be due to direct irritation of the nervous system by shock or excitement determining the toxin to that system, just as a wetting determines arthritis of the upper or lower extremities as the case may be. And further on he says: "But arthritis is never the first result of fright, and chorea is never the first result of chill." Exactly so, for fright causes depression and collæmia, which is the opposite condition to arthritis; and chill by causing a fall in the alkalinity of the blood clears the uric acid out of it into the joints, thus producing arthritis, which is the opposite of collæmia, and chorea.

These considerations explain also a point which some regard as exceptional and mysterious, namely, why, if uric acid is the cause of arthritis there is none in conditions of anæmia and debility, such as splenic leucocythæmia, when the blood and urine are full of uric acid.

But the incidence of arthritis depends upon whether the blood is a good or bad solvent of uric acid, is taking it up from the tissues or throwing it into them; and in all these conditions of anæmia and debility the only reason for excess of uric acid in the blood is that its powers of dissolving and holding it in solution are increased; and this is exactly the condition which we desire to produce when we want to cure arthritis.

On the other hand, it is not very difficult (and it has been done or has done itself in many of the cases mentioned) to drive some of the uric acid out of the blood into the joints and produce arthritis; hence the commonly observed alternation of anæmia and rheumatism; with many girls of the present day, life is made up of such alternations for some years.

It is only fair to say that Dr. Churton adds to the above quoted lines "unless fear or brain excitement accompanies the chill"; but I am concerned with the rule and not with the exception, and the rule is that fear causes collæmia and depression and chill clears the blood of uric acid either locally or generally, and may thus produce arthritis or inflammation of any fibrous tissues.

I now mention in illustration of some of these points a case under my care. It is that of a girl, aged 16, admitted into the Metropolitan Hospital with her third attack of chorea on March 14, 1897. There is no sign of endocarditis, either recent or of old standing.

Her mother is a sufferer from megrim, and one of her mother's sisters had chorea in childhood.

The patient herself suffers from sick-headache (uric acid headache) from time to time, and had several bad attacks in rather quick succession just before this last attack of chorea came on.

The determining cause of this last attack seems to have been an injury resulting in a severe cut on the thumb of the right hand, which formed a rather ugly wound at the time of admission.

Here, then, we have a shock as the determining cause, and we have this supervening upon the passage of a considerable amount of uric acid through the blood, as shown by the frequently recurring headaches.

On admission she was noted as being extremely anæmic, and presented all the signs of debility and exhaustion.

She was in service in what is known as a "hard place," and this would undoubtedly produce fatigue and collæmia; and we know that collæmia at her age, three years after the year of greatest growth (see chapter xii. and fig. 59), would of necessity be severe, and would, as is common in girls of her age, produce chlorosis; further, the collæmia would be signalised by exactly what we find in her history—severe and rather frequently recurring headaches. It may not be without interest to remark in passing that epilepsy very frequently begins in girls just at the age of this patient, and no doubt it does so as the result of causes similar to those that rendered her headaches more frequent and troublesome. Epilepsy also is a disease closely associated with collæmia, and may apparently originate in a fright or shock. Then the progressive fatigue, collæmia and anæmia would be certain to react on the nutrition of the muscles and the heart and weaken them.

This, then, was her condition when, on March 9, a china basin fell on her hand and cut it severely.

This caused a considerable shock, which intensified the collæmia by further upsetting nutrition. The collæmia would have raised the blood pressure and caused headache, but the heart had now failed before its accumulating misfortunes to such an extent that it was no longer able to keep up the pressure; and so there was no headache, but the choreic movements soon began, for there was collæmia, and collæmic blocking of the capillaries of the brain was favoured by the very weakness of the heart, which rendered headache impossible (see remarks on antipyrin on p. 254).

The pulse on admission, five days later, was 144, with a temperature a little above 99° F., but the very violent movements may

quite account for this and the signs of exhaustion, which were most marked.

She was given injections of morphine on the first day and then put on a small dose of arsenic; and in two or three days was much quieter and even able to speak a few words.

The movements continued, but less violently, for many weeks, but by the end of April they were almost gone and she was allowed to be up for a little; she was continuing the arsenic and gaining weight.

She was still, however, decidedly anæmic, say blood decimal by colour card ·35 to ·4, and had a quick pulse.

Her previous attacks of chorea, first at 10 years old and second at 12 years old, were much less severe than the third, and this is interesting, as she would probably have less uric acid available before her year of greatest growth than after it; and I cannot help thinking that if she had been on a uric-acid-free diet from the date of her second attack she would now have escaped the collæmia, anæmia, headaches and chorea.

For an interesting case in which chorea apparently followed on depression, hysteria and excessive irritability (these being all signs of collæmia and appearing during menstruation, its frequent cause), and in which embolism and thrombosis of certain vessels were found after death, see *Brain*, July, 1889, p. 175; and for a case in which chorea came on as rheumatic fever left off, that is, when there was almost certainly collæmia, see *British Medical Journal*, 1894, vol. ii., p. 1227. But chorea follows other acute diseases besides rheumatic fever, for every acute disease in a child is followed by post-febrile collæmia (see also article in *Progrès Médical*, April, 1888, p. 301). These considerations lead me to ask the question, Is chorea a collæmia, some of the effects of which are intensified by cardiac failure, this etiology explaining both its relation to arthritis and the action of the drugs that cure? Further observations show that heart failure is a constant factor in the onset of chorea and that by the time rest and tonics have restored the heart power, and so raised the blood pressure and improved the circulation in the brain, the chorea is at an end.

With regard to diagnosis I have little to say. When I see an arthritis which appears to have originated under conditions which might have precipated uric acid, and can find no other obvious cause, I treat the uric acid and judge by the results; if the trouble is relieved by solvents there is no room for doubt.

I have occasionally been misled, especially by malignant and

other new growths; and perhaps one should view with a certain amount of suspicion arthritis in a single joint, standing alone and yet not having exactly the characters of regular monarticular gout; similarly, in what appears to be rheumatism standing alone in one single joint, we must not forget that there are some other things besides uric acid which may cause such trouble.

In one or two cases of deep-seated new growths the myalgic and neuralgic pains have for a time resembled the work of uric acid, and, strangely enough, in some of these cases salicylates have, even for a day or two, markedly relieved such pains though due to new growths; possibly they have exerted an influence indirectly through the blood pressure, though even in new growths the presence of uric acid may increase a local irritation, and its removal will at least do no harm.

I notice, in *St. Bartholomew's Hospital Journal*, December, 1899, in an article on "Primary General Acute Gout" (by which is meant, I gather, polyarthritis, clearly due to uric acid coming in middle life with a history of rheumatism preceding it), that Dr. Parker attempts to explain the (for him) difficult questions: (1) Why so many of these cases gave a history of rheumatic fever (28 per cent.); (2) Whether rheumatism predisposes to gout and gout to rheumatism; and then goes on to say, "Are we, with Dr. Haig, to regard both gout and rheumatism as manifestations of an uric acid diathesis?"

I trust that none of those who may do me the honour to read my writings will think that they are with me in believing in any such product of ignorance as "the uric acid diathesis."

As I have already said, gout is rheumatism and rheumatism is gout, for the arthritis in both is clearly due to uric acid, and this is the only pathology that will satisfactorily explain all the conditions met with, while the above is a good instance of the difficulties in which others find themselves in trying to work out any other explanation of the facts that nature presents.

But no situation is made clearer by the mere substitution of one unknown factor for another. The word "diathesis" is but a cloak for ignorance; away with it, and substitute that which can invariably be demonstrated, namely, poisoning by flesh and tea or similar alkaloid-containing substances.

Has, then, the sufferer from arthritis nothing to fear from the uric acid he forms? No doubt he has, for his joints having been injured will long be liable to further irritation from comparatively slight causes, and if they contain any urate residues these will

attract fresh urates from the blood and tissue fluids at every opportunity (see uric acid filter work in chapter v.); but if these people had never eaten flesh or swallowed substances rich in alkaloids, which we shall discuss in the next chapter, they would have had no arthritis either in early, middle or late life, but their joints at 60, 70 or 80 years would, except for accidental traumatisms, be as clear and free from disease and disorganisation as at 6, 7 and 8.

Food poisoning is a reality which can be demonstrated in every case, its effects measured and its progress stopped. Better still, its beginnings can be prevented, and when this has been done the phantom diathesis will have no more dark corners in which to hide.

As regards treatment, it should never be forgotten that there are two ways of curing arthritis: (1) Elimination, as by salicylates, and (2) retention, which clears the blood and prevents more uric acid being brought to the irritated joint structures, and this is the action of iodides, guaiacum, sulphur, sulphates, sulphate and calcium waters, &c.

Elimination is useful in acute conditions, and when it is completely successful in relieving pain and reducing temperature it affords positive evidence that the arthritis was due to uric acid, for in arthritis due to other things elimination of uric acid has no effect.

Retention is useful only in chronic cases, when the irritated joint is acting as a uric acid filter and attracting and retaining all the uric acid that comes near it in the blood and tissue fluids, and with each increase of uric acid in the joint there is an increase of pain and trouble. But if the retentive drug clears the blood of uric acid there will be less to get caught up in the irritated joint, and so the irritation has time to subside; and thus chronic arthritis can be relieved by drugs which cause retention, or a full meat and wine diet, which produces the same result.

I think that cases of arthritis can best be considered as falling into three groups:—

(1) Acute.
(2) Chronic.
(3) Chronic with marked debility and anæmia.

In acute cases with fever, salicylates have, as a rule, only to be given freely to be given successfully.

They must be given in a sufficient dose because, other things being equal, the amount of urate eliminated depends on the amount of salicylate in the blood to combine with it. I have seen gr. x. of

salicylate of soda given three times a day in acute rheumatism without the smallest effect, when gr. xx. every two, three, or four hours promptly relieved.

Salicylate of ammonium is by some considered to be less nauseating than the sodium salt, and for the reasons previously mentioned it has probably some advantages over it as regards the elimination of uric acid, especially in subacute or chronic conditions. The same applies to salicylic acid, aspirin or novaspirin.

There are but few reasons for not giving a good dose, and the head symptoms which the salicylates produce are generally trivial. If they do cause a little depression, what is that to the depression of a prolonged attack of acute rheumatism? And it seems that at least a part of the depression they have been credited with is really due to impurities which we are gradually learning to eliminate (see an interesting article by Dr. Lees, *Lancet*, 1893, vol. ii., p. 190).

When the temperature is not high you must keep the patient cool, and on no account allow perspiration, as this will quite upset the action of the salicylates. In these circumstances (subacute cases in hot weather) you must not only clothe very lightly, but you may also give small doses of the mineral acids two or three times a day in alternation with some of the doses of salicylate before their best action in removing uric acid and relieving arthritis is obtained. This treatment will prevent the salicylates from causing depression, as their depressing effect, when not due to the above-mentioned impurities, is generally the result of meeting a large amount of uric acid in the body and sweeping this into the blood, where, in the absence of much fever and in the presence of perspiration and debility, it may meet with much alkali with which it combines, producing collæmia, with its depressing effects on circulation, nutrition, and metabolism.

These effects of the salicylates are thus due partly to the quantity of uric acid met with and partly to the meeting of this uric acid with much alkali in the blood, producing collæmia.

I have seen salicylates produce severe collæmia, with unpleasant cerebral and aural symptoms, perhaps heart failure, with collapse, delirium, or mania (see chapter viii.), when given with alkali, or in cases where the fever was not high enough to keep up the acidity of the urine and keep down the alkalinity of the blood, or again in cases where the patient was kept under heavy clothing. And this without much relief of the arthritis, perhaps even its accentuation.

My own practice is, therefore, in acute cases to give plenty of

salicylate, and to see that the patient is in no danger of perspiration; in less acute cases, to keep the patient distinctly cool, and even to give some acids if the weather is hot; and with these precautions the arthritis is generally quickly relieved, and no other troubles occur.

Aspirin, a combination of salicylic and acetic acids, is very useful in subacute conditions, as the acid radical keeps down the alkalinity of the blood and prevents uric acid combining with alkali, and the dose is the same as that of salicylate of soda. Very good results with aspirin have also been reported in pleurisy with effusion (no doubt rheumatic) and in pericarditis (see *British Medical Journal*, 1902, vol. i., Epitome, p. 12); and it is in such serious conditions, causing fall of temperature and depression, that the greatest good may be expected from it.

Another useful method is to give salicylic acid and pulv. opii co., say 5 gr. of the latter and 10 gr. of the former in a cachet. This acts in precisely the same way as aspirin, and one thing will agree in one case and another in the other. Chronic cases need all the help we can give the salicylate by cold, acids or other drugs; acute cases are easily cured by salicylate alone.

It is most interesting the way in which the power of salicylates is increased by combining them with acids or substances which raise acidity (opium and ammonia), and their action as solvents of uric acid gives the only explanation of the facts (see my paper in the *Medical Record*, New York, December, 1907).

When salicylates, given with proper care, and in satisfactory quantity, relieve the arthritic pains and reduce the temperature somewhat, but it still does not fall to normal, we may consider the possibility of enteric or some other fever, of which the arthritis was a mere complication in an arthritic subject.

Where salicylates fail either to relieve pain or reduce the temperature to any noticeable extent, after all conditions have been made favourable to their action, and aspirin has also failed, the possible presence of pyæmia or septic arthritis should be considered.

If salicylates act quite satisfactorily, relieving the pains and bringing down the temperature, they should be continued for a time (weeks, perhaps months) in small doses to clear out as much as possible of the stores of uric acid and prevent a relapse, for if any urate (even a quite microscopic quantity) is left in the affected structures it will act as a uric acid filter and attract more from the blood and fluids as soon as the solvents are left off. The patient should, of course, never be allowed to return to a diet which will

introduce any further xanthin or uric acid. He is put on a milk and cereal diet during the fever; let that diet be continued with the addition of cheese.

The treatment of morbus cordis, so far as it is due to valve or pericardial lesion, has hitherto comprised little beyond the use of tonics and stimulants, but it is evident from the case of A. S., mentioned above, that we must be very careful not to use these tonics and stimulants too soon or while there is any heat or irritation remaining about the valve, or we shall only make it blaze up again, and, precipitating more urate upon it, make matters worse.

While valve lesions are recent, I think we can hardly do better than follow the treatment suggested by Dr. R. Caton (*Lancet*, 1895, vol. ii., p. 399), which consists in giving gr. x. of an iodide three times a day, in addition to salicylates, and placing repeated small blisters on the chest wall over the damaged valves.

The salicylates effect the elimination of uric acid, while the iodides keep it from combining with alkalies and raising the blood pressure, which would increase the work the heart has to do.

Recently I have got equally good results by leaving out the blisters and replacing them by painting over the cardiac area with salicylate of methyl, covering this with gutta percha-tissue, and over this an ice or iced water bag; and the same treatment can be applied to any local trouble which is sufficiently near the surface to be affected by local treatment, using either salicylate of methyl or salicylate ointment and ice, the ice acting the part of an acid and increasing the solvent action of the salicylate (see also treatment of pneumonia, chapter ix.).

We must rest the valves as much as possible, and must do all we can to restore their normal alkalinity; and, lastly, I think we must keep on with salicylates for several months at least, to protect them from the evil effects of exposure to cold or the accidental use of acids or other things that affect the solubility of uric acid, and also to make as sure as possible of sweeping out every atom of urate from the affected fibrous tissues (see previous remarks, especially those in chapters ix. and xv.).

We now come to the cases of chronic arthritis in which digestion is sound, food is well taken, there is no anæmia or debility, and the temperature is nearly normal, except, perhaps, for occasional evening rises.

These, again, are cases for the salicylates; they do not represent the most favourable condition for their eliminative action, but with time and perseverance they will do good—probably more good than anything else.

Here salicylate of soda may be given along with an iodide or other retentive drug to keep the urate from combining with alkali and causing depression, or acids or opium may be given along or concurrently with it for the same purpose.

Salicylate of ammonium may do better than the sodium salt, or aspirin or salicylic acid may be better still, given in cachets, with small doses of pulv. opii co., to make the conditions favourable for it.

At first, under these chronic conditions when there is no fever to help the salicylate, ordinary diet—meat, fish, egg, and wine, or beer—should be continued; but an attempt may be made to alter the diet when the salicylates have been in action some time, the pains are better and a considerable amount of uric acid has been removed from the body (for salicylates remove that which is introduced each day as well as that which is retained in the tissues).

This should be done slowly and gradually, with care not to lower nutrition or upset digestion or increase the alkalinity of the blood.

Substitute breadstuffs, milk and cheese for flesh, fish, fowl and eggs, as near as may be in exactly equivalent (albumen) values; continue the beer or wine as before, or very gradually reduce them, substituting acid vegetables and fruits to prevent any fall of acidity, and thus avoid everything that may make the conditions unfavourable for the salicylates.

We must not forget that these drugs not only do good under right conditions, but do actual harm under wrong conditions, as in the cases previously mentioned.

When the changes have been completed, continue the diet and the salicylates for months and years; one and a half, two, or even three years may not be too long a time to allow for clearance of urates from the tissues, and I have had a good many patients who have willingly gone on for such a time and have expressed themselves greatly pleased with the results.

To expect that salicylates will act in chronic conditions with anything like the same power and promptitude that they show in the favourable conditions of acute disease is to expect the impossible. What we have to do in chronic cases is to make the conditions as like those of acute cases as possible and to continue the salicylates.

On the other hand, to be discouraged by the small effect of the salicylates without understanding its causes, and to give up these drugs in favour of other treatments to be tried one after the other, is to court failure.

Statistics clearly show that salicylates have done great good in rheumatism, diminishing its death-rate, and greatly diminishing

its serious complications (see Sir Douglas Powell, *Lancet*, 1900, vol. i., p. 922), and I am constantly pointing out that when its relations to cold and heat, to acids and alkalies, are more generally recognised, still better results will be obtained; but even the above observer still advises the use of salicylates with alkalies and woollen wrappings; conditions in which they cannot possibly produce their best effects, and this may account for his opinion (previous reference, p. 921) that acute rheumatism is still a matter of four to six weeks.

With regard to this my friend, Major W. G. Beyts, tells me of some excellent results he has obtained in acute rheumatism by the application of cold. In some cases he has applied snow or cloths wrung out of ice-cold water, in spite of the obvious terror of the patient; but these, with salicylates, have done nothing but good, and patients only need a few hours of experience to see that cold is really their best friend and soon wish to have it applied to all their joints. These results are very interesting, and completely confirm my deductions from the chemistry of the subject.

A case of my own may also be mentioned. A boy was admitted under my care in the Metropolitan Hospital suffering from arthritis, chiefly in the left knee. He was given salicylate, and the joint was enveloped in cotton wool and a bandage (the very opposite to Major Beyts' treatment). When I came to see him a day later the temperature had not fallen and the pain in the joint continued, so that the question was raised whether the arthritis was rheumatic. On seeing the joint I at once ordered the removal of the warm wrappings and substituted a cradle to keep it cool. In another twenty-four hours the salicylate had cured it and all doubt as to diagnosis was at an end.

Lastly, we come to the chronic cases of arthritis associated with anæmia, debility, dyspepsia and generally feeble nutrition.

Here we have the most unfavourable condition for the eliminative action of salicylates, and in such cases they may be expected to fail and should not be given until conditions have been made more favourable to their action.

The first thing to be done is to improve digestion, to increase appetite and feed up, to diminish the anæmia with tonics, as iodide of iron, iodide and cinchona, arsenic, acids, chloride of calcium, guaiacum, or urea, anything and everything that will improve appetite, digestion, nutrition and the blood condition.

I notice that Dr. Kent Spender records in the *British Medical Journal*, 1902, vol. i., p. 697, a case of "Chronic Rheumatic Arthritis" which was greatly benefited by a three months course of opium—$\frac{1}{12}$ gr. every three or four hours. This no doubt acted like

some of the retentive drugs named above, kept the blood relatively clear of uric acid, prevented the uric acid filter action of the affected joints, and so allowed the pain to subside.

Sometimes these measures will succeed if combined with change to a bracing mountain climate, and then, when digestion is good and blood fair, we may give the salicylates as in the previous class of chronic cases without debility, and later on alter diet also.

Are we to prescribe a uric-acid-free diet in cases of chronic arthritis with debility? As a rule I say no, for the only effect will be to increase collæmia, anæmia and debility, the exception being, perhaps, in cases where a patient can digest and prefers the bread-stuffs, milk and cheese of a uric-acid-free diet to anything else.

As a rule we must use tonics, change of air and ordinary diet at first, just as I have advised in the treatment of chlorosis in a previous chapter; and then if digestion, nutrition and blood improve, go on to salicylates and uric-acid-free diet as in the less debilitated cases.

Diet alone goes to the root of the matter by cutting off the supplies of the poison from without; but, as with all other treatment, there are certain conditions in which it cannot and must not be used.

There is absolutely nothing, however, to prevent its use in the bringing up of children of gouty and rheumatic families, who have as yet no active disease. Here it can be begun as weaning is being carried out, and such children will develop far better than others.

I do not need to quote cases in illustration of this, for instances may be seen any day in the cottages of country peasants.

Too much credit for the result has always been given to the air, too little to the frugal fare which poverty has enforced, and thus has presented them with a blessing which wealth cannot buy. But even in cottages this magnificent health is not so common as it should be, for tea has spread even faster than meat, and this has been closely followed by the meat extracts and decoctions.

Gout in this country used to be a disease of the rich, and in poorer countries this is still the case. The poor lived here, and still live elsewhere, on the diet I advocate, and in proportion as they are xanthin-free do they escape from the arthritis due to uric acid. This is sufficiently evident to all who have travelled in foreign countries, and may still be seen even in parts of Scotland and Ireland, and it would be yet more evident if pulses and tea were everywhere as expensive as flesh, and flesh has unfortunately been greatly cheapened during the last thirty years.

Diet combined with or in sequence to drugs will not only stop

the progress of arthritis, but in the same way arrest, and allow the repair of, the more serious endocarditis.

Here we cannot see the lesion and can only judge from its external signs, but I am of opinion that after the treatment by iodides, salicylates and blisters has had its turn, and produced its effects, diet should be continued for months and years, and in cases where this has been done, some of which I have seen with Dr. Gayford (whose record of an interesting case I give on a previous page), the physical signs showed no increase of lesion, but rather that it was being slowly diminished.

And I have had reports of children, seriously affected both in joints and endocardium at an early age, who have yet developed into vigorous and healthy adults on treatment similar to that advised above.

This brings me to local treatment, already mentioned in the case of the heart, and with this exception I consider local treatment a matter of very small importance as compared with such things as diet and nutrition. One of the things we must make certain of, with our local treatment, is not to do harm nor to hinder digestion and nutrition and the action of our important drugs. For, obviously, local treatment does not go to the root of the matter nor control the disease; it merely palliates certain symptoms, and to allow any such treatment to interfere with the main treatment is to sacrifice the whole to the part. I consider, therefore, that massage, hot air and hot water must never be allowed to produce or increase general debility.

In acute arthritis, where there is gastric upset, with vomiting, or where salicylates by mouth are not well taken or cause gastric trouble, salicylate of methyl painted over several joints or a large surface will relieve and cure in much the same way as if taken by mouth.

In chronic arthritis some xv.-xxx. drops may be painted over the most troublesome joint night and morning or more often, and covered with gutta-percha tissue, kept in place with a bandage, and an icebag or cold bottle placed over the gutta-percha.

This may be done as an aid to the salicylate by mouth, or while tonics are being given to pave the way for salicylate. Where acute arthritis has subsided and salicylates are being continued, while one joint remains perhaps specially tender and puffy, a few small blisters or a touch with the actual cautery do as much as anything to relieve the local swelling and tenderness and enable the joint to be brought into use.

Major W. G. Beyts records that an ointment of lanoline or vaseline containing xx. or xxx. gr. of salicylate of soda to the ounce may be very useful not only in uric acid arthritis, but also in traumatic arthritis (sprains and injuries) in those who consume meat and tea, for in those who are full of urates a traumatic arthritis promptly becomes a uric acid arthritis. The ointment is to be spread thickly over the seat of the injury and an icebag or ice cloths over that.

Then there is the local application of heat, which may undoubtedly be of use as regards a single joint, or a series of joints which are rebellious to other methods or hang back from a general improvement.

For such single joints I have no objection to it, though it must never be forgotten that general heat to the body, as a whole, is a treatment by alkali, and as such is absolutely incompatible with salicylates. Any attempt to combine the two will only lead to disaster, and even a single joint will probably not be improved by heat while salicylates are in the blood (see cases previously mentioned).

In certain cases general treatment by heat to the whole body may be used with advantage, and the arthritis may improve under its local and general effects, but it is a treatment by alkali and promotes the removal of urates just as an alkali does (see *British Medical Journal*, 1899, vol. i., p. 853), and like this also it is more or less decidedly depressing, causing or increasing anæmia.

Local cold, on the other hand, will, as pointed out by Dr. Ewart (*British Medical Journal*, 1899, vol. i., p. 854, and *Lancet*, 1899, vol. i., p. 955), often relieve the pain of chronic arthritis, and this is not incompatible with the administration of salicylates but aids their action. Dr. Ewart apparently used rubbing of the surface with a block of ice or the application of an icebag.

In several cases I have found this local use of cold do good, and I look upon the increase of arthritic pains, which so often occurs on getting warm in bed at night, as an indication for it.

With regard to this use of cold, we must not forget that apart from salicylates, cold interferes directly with the solubility of uric acid, throwing it down in colloid form from solutions, and its relieving pain in chronic cases reminds me of Dr. Pfeiffer's experimental observation on himself, previously mentioned, that acids, which act like cold, diminished the local irritation of injected urates, while alkalies increased it. All chronic arthritis with debility is urate irritation under alkali, for with increasing failure of nutrition the blood and tissue fluids become increasingly alkaline, and the

increase of arthritic irritation may be due to uric acid previously deposited coming again into solution. This should, of course, eventually end in complete solution and removal of the urate and cure, and I think that this does occur in some very chronic cases; but during this removal the pain and damage to fibrous structures and also to blood and general nutrition may be great, so that the patient dies of debility or some complication.

In any case the action of cold is the parallel of that of the iodides, tonics and certain mineral waters mentioned above. It favours the best action of salicylates, so that an icebag is the best local application while these drugs are being given, whereas heat not only hinders their action but makes them do harm.

While urates are present or liable to recurrent precipitation on the damaged structures with the daily, almost hourly, fluctuations in the alkalinity of the blood, we may have a progressive condition of irritation, leading to ever increased fibrosis and stiffening, and that whether the original condition was uratic or traumatic, for in those whose fluids are full of urates every traumatism of fibrous tissue is sure to be irritated by their presence and recurrent precipitation, so long as the seat of injury is less alkaline than the blood and tissue fluids of the body. For in this condition it acts as a uric acid filter as regards the blood and tissue fluids, giving up uric acid to them if they are very alkaline, taking it up from them if they are not.

Now the effect of massage on an injured fibrous tissue is to flood it with fresh blood and to bathe it through and through with fresh alkaline serum, as shown perhaps by considerable increase of swelling after the massage.

The swelling, however, subsides, and the serum is taken back into the circulation, and it not only takes with it some of the urate that caused the irritation, but also some of the acid salts that rendered the fibrous tissue a seat for urate accumulation; hence it comes about that repeated massage every two or three days for a couple of weeks may not only remove the urates which are the cause of the irritation in the fibrous tissue, but may render it as alkaline as the blood and tissue fluids in general, and therefore no longer a seat for chronic and recurrent retention of urates; thus it breaks through the uric acid filter action, and this may be the end of the trouble.

Here is another reason for the rapid and satisfactory repair of wounds and injuries in such nations as the Turks, who live on an almost uric-acid-free diet: they have not only, as already pointed out, a greatly improved circulation owing to absence of collæmia and

a better supply of alkali for damaged fibrous structures, but they have also less uric acid to be precipitated upon these structures and keep up the irritation. Then where those living on a uric-acid-free diet have required operation, the surgeons have nearly always remarked on the rapid and satisfactory repair of the wound. These people get well simply and naturally without the opium and subsequent massage that are so often required by the urate-laden meat eater.

Do we not here see at least a partial explanation of the good results produced by so-called "bone-setters," who break down and subject to massage the fibrous tissues round an old traumatism?

For an interesting case where gout was cured by massage, see a paper in *Edinburgh Medical Journal*, 1898, vol. i., p. 561, by Dr. G. W. Balfour, who suggests that the massage cured or prevented the thrombosis; but I think it is much more probable that the massage really cured by flooding the affected tissues with fresh alkaline serum, which would increase the solubility and aid the removal of uric acid, thus bringing its action into line with that of alkalies and salicylates, which cure gout by eliminating uric acid.

When joints are distended by fluids and surrounded by much puffy fibrous tissue, a horse shoe blister, or a series of smaller blisters, will often do much good by removing the fluid; it thus relieves the pain due to tension, and may enable the patient to use the limb once more, and we may then be able to produce some improvement in general health, which it is so important to do in chronic and debilitated cases.

I am much interested to see in reference to what I have said in this chapter and in chapter x. that Dr. T. Stacey Wilson says in an article "On Colon Catarrh," *British Medical Journal*, 1902, vol. ii., p. 1764: "The key to the treatment of this disease is in my opinion the recognition of its relation to gout." The result is that he uses salicylates and uses them with success, and this, I may remark, is the key to the treatment not only of colon catarrh, but of all catarrh, rheumatism or irritation by uric acid in every fibrous tissue throughout the body.

My treatment of rheumatism is in a word salicylates followed by alteration of diet; elimination followed by stoppage of introduction; and where conditions are unfavourable to the best action of these powerful drugs, I devote my whole attention to making them favourable.

Acute rheumatism is, like gout, a trouble due to retention of uric acid; it is therefore relieved by solvents. In very chronic cases

with anæmia and debility it may be associated with collæmia, the irritation being kept up by the uric acid filter action of the irritated tissues and local deposits, and this condition may be temporarily relieved by precipitants and a highly nourishing and stimulating diet, which clear the blood of uric acid and stop this action. The rule is, troubles that get worse with solvents get better with precipitants, and *vice versâ ;* but when an arthritis is affected by neither, some cause other than uric acid should be looked for.

CHAPTER XVII.

Treatment.

"The proof of the pudding is in the eating," or rather the proof of the poisonous nature of flesh and tea lies in the effects of refraining from their use, and the best possible tests of the truth and stability of the above considerations are the results obtained by applying them. It matters little to those who suffer whether the poison in the blood is uric acid or xanthin; but it matters everything if, by altering their diet and getting nitrogen from one source rather than another, they can free their blood of poison and themselves of the diseases it produces.

Many volumes of theory did not suffice to prevent one of my headaches, but, ascertaining that they were due to poisoning by meat and tea, prevention became both certain and simple, and relapse is a mathematical certainty if these poisons are again taken in any form.

It has now been definitely proved that flesh eating is fatal to endurance, just as Shakespeare long ago suspected it was bad for the wits.

The record of some experiments in which abstainers from flesh (and in some instances from other sources of uric acid as well) exhibited more than twice the endurance of flesh eaters is given by Professor Irving Fisher in a paper on "The Influence of Flesh Eating on Endurance," *Yale Medical Journal*, March, 1907 (see also Professor Fauvel, "Monographies Cliniques," December, 1907, p. 42).

In the last edition of "Diet and Food" I noted the converse fact that the Japanese, brought up on a fleshless diet, at once experienced lethargy and fatigue when meat was added to their food.

The above-named paper, while substantiating in the most com-

plete and satisfactory manner all that I have for years been saying on the physiology and pathology of fatigue, though mentioning my explanation of the facts and giving me credit for many good results in patients treated with the uric-acid-free diet, yet suggests that I estimate too highly the quantities of proteid required (p. 14 of pamphlet).

Then referring to my theory of collæmia as a cause of high blood pressure, Professor Fisher says: "Observations actually show that persons possessing great endurance often have low blood pressure. This is true, for instance, among the subjects of the present experiment at Battle Creek." This is interesting, for it is probably at Battle Creek that the most completely uric-acid-free diet is practised, as my books have long been in use there.

It is obvious that the writer of this paper finds himself in considerable difficulties once he gets outside the limits of the uric acid theory of causation, as he has little to offer his readers except the useless generalisation of nameless "fatigue poisons."

As to quantities, all my patients have my leave to live on less proteid if they can do so without loss of strength, endurance and blood colour, and it must be remembered that all these can be kept up for a time on deficient proteids with the aid of stimulants, *e.g.*, fruit, cold, or a bracing climate; but I was forced to fix the standard I use by the fact that those who took less eventually broke down.

It is not without interest in this connection that when, as frequently happens, a husband and wife take up diet simultaneously, the former, leading a fairly active life, can eat the more bulky foods without much difficulty and soon becomes strong and well-nourished upon them, while the latter, keeping in the house all the morning, and perhaps taking only a drive in the afternoon, cannot manage the increase of bulk, remains debilitated and anæmic, and eventually has to add egg, fish or meat to avoid collapse, thus failing to get the full advantage of freedom from uric acid.

I must have seen ten or a dozen instances of this in the last few months, and yet if, as recent experimenters assert, my quantities are too high, the women should be well nourished, while the men are overfed. I, on the contrary, believe that their quantities are too low, and that, given longer time, many of those who attempt to live on them will break down (see *Edinburgh Medical Journal*, December, 1907).

I occasionally see people who say that, though they are doing well on the diet, they are not taking nearly the quantities I advise; but when it is possible to collect their urine and estimate urea, the

facts often fail to bear out their assertion; and one frequent cause of this mistaken idea of quantity is under-estimation of vegetables and fruit. Patients often tell me that their vegetable and fruit for the day is only some 10 oz. or 11 oz., but on going into details it comes out that they are eating one, possibly two, apples after each of the three chief meals, and potato and other vegetable with two of them. Now, quite a moderate apple will weigh 3 oz. to 4 oz., and larger ones 5 oz. to 6 oz., and potatoes are equally heavy. It follows that in the above cases the vegetable and fruit taken are nearer 30 oz. a day than 11 oz., and these people are underestimating their albumens by 160 gr. and their urea by 50 gr. to 60 gr., and are therefore nearer my quantities than they suspect.

It is interesting to note that the men, who at once do well on the diet, do not clear out their urate stores and have no early depression. The women, who cannot take the quantities, clear out at once and have early depression, but this clears off if they continue, and then if they can increase these quantities they also do well. But all who have much urate retained must clear out some time, and so the men who do well at first may have debility, anæmia and depression later. Now, such debility and anæmia, coming perhaps after several years on diet, are often thoughtlessly credited to the "impossibility of living on such a low diet," regardless of the fact that many of our ancestors, even in these islands, lived on it for hundreds of years, and that a majority of the race in other parts are living on it still, and when they get enough albumen are neither debilitated nor anæmic. And yet it appears that I am accused by at least one of the above-named professors of ordering for my patients too much albumen.

Obviously the one accusation neutralises the other, for it cannot be a "low diet" and also contain excess of albumen, and the real explanation is simple, for the debility and anæmia, whether coming early or late, are due to the accumulated urates of the old flesh and tea diet.

The diseases treated of in the first fourteen chapters are more or less directly due to excess of uric acid in the blood, those in the fifteenth and sixteenth are due to this excess being driven out of the blood into certain fibrous tissues. The diet treatment of these diseases is keeping the body and blood free from an excess of uric acid, and we have now to consider the way in which this can be done.

Uric acid is met with in excess in the body and blood chiefly from three causes: (1) It has been introduced in excess by the consumption of articles of food such as meat, eggs, fish, pulses,

mushrooms, asparagus, tea, coffee, cocoa and guarana, which contain it or other equivalent members of the xanthin group; or (2) because so much nitrogen is taken that the uric acid formed out of it in the relation to urea of about 1—35 is, owing to the high acidity which the salts and other products of nitrogenous metabolism produce, not all excreted, and a store is gradually formed in the body to the extent possibly of from 52 gr. to 400 gr. in a year; (3) the high acidity which results from the taking of much animal food prevents the excretion of the uric acid introduced with this animal food, as well as of that which is formed out of its nitrogen along with a certain quantity of urea. In a word, animal food increases the introduction and formation of uric acid, and at the same time prevents its elimination, and the alkaloids of tea, coffee or cocoa and certain similar vegetable products, *e.g.*, those contained in the pulses, act in the same way.

Speaking of guarana reminds me that it is probably by its nitrogenous or xanthin elements that it cures sick headache (uric acid headache), because, a dose of uric acid itself will cure a uric acid headache, and the first effect of such a dose, and probably also of ammonia and nitrogen in other forms, is to clear the blood. I remember years ago, before I began to study medicine, pointing to a plate of meat and saying, "My headache will be all right when I have eaten that." I now know that the nitrogen and salts so introduced diminished the alkalinity of the liver, started a uric acid filter there, and so cleared the blood of the uric acid that was causing my pain, a rise in the acidity of the urine following and showing what had occurred. But I would earnestly warn any fellow-sufferer against treating his trouble in this way, for I believe it to be a most dangerous course; the uric acid thus cleared out of my blood was not cleared out of my body—more was introduced—and for years afterwards I suffered with most terrible headaches; while the urates thus stored up were passing through the blood, and I believe that damage was then done to my heart, vessels, liver and other structures which no subsequent change of diet has sufficed to wipe out.

I would say, further, do not under any circumstances resort to caffein or guarana for relief; they are practically uric acid, and present relief is obtained at the price of future suffering. I have seen many cases in which the employment of these substances for some considerable time for the relief of headaches, &c., has been followed by deplorable consequences.

With regard to diet we have seen that as flesh diet increases the introduction of uric acid, it increases the formation of uric acid,

and its salts diminish the excretion and elimination of uric acid. A milk and vegetable diet, provided that no excess of albumens is taken, introduces less uric acid, causes the formation of less uric acid (because urea is unnecessarily high), and its salts promote the free elimination of all uric acid that is introduced into or formed in the body. Thus we see (p. 16) that I excrete now 12 gr. of uric acid, of which 10 gr. are formed in the body and 1·9 gr. are introduced ready formed, while a fraction of a grain is accounted for by the excretion of urates previously stored in my body. With this low formation and introduction of urates I have rarely any excess in my blood, and consequently suffer little or not at all from headache and other signs of such excess.

In former years on ordinary diet I used to excrete 500 gr. of urea, and in the above proportions I must have formed 14 gr. of uric acid and introduced at least 5 to 6 gr. ready formed in my food. It is easy, then, to see why I often had an excess of urates in my blood, and suffered from the effects of such excess, namely, defective capillary circulation, high blood pressure, headache and mental depression. I believe that the ordinary diet section of mankind may possibly introduce as much as 3 or 4 gr. of uric acid with each meal, or 9—12 gr. in a day or more, and sooner or later will suffer in proportion.

In Persia, where only the rich eat meat, gout has come to be known as the rich man's disease (see *Proceedings of the Royal Medical and Chirurgical Society*, third series, vol. v., p. 46, where this interesting fact is contributed to the discussion on my paper on the iodides by the physician to the Shah), and we have already seen that the children of the rich are in this country specially liable to anæmia, no doubt due to excess of meat in their food, and in chapter xvi., that M. Bouchard considers that such children are liable to many troubles, including migraine and acute rheumatism, and that their anæmia and collæmic circulation can be seen at a glance.

We have, then, two things to do to attain our object: we must cut off all food which contains uric acid, and is not absolutely necessary, and we must not take more nitrogen than is required to keep our urea at the physiological level of 3·5 gr. per pound of body weight per day, or 3·0 gr. per pound for sedentary adults of middle age.

With regard to cutting off we may at once forbid tea, coffee and cocoa, or permit them only in the smallest possible quantities as flavourings, as some Eastern nations take tea not only weak but made with water which is only warm. We may cut off such

animal food as contains uric acid, and give only so much of the less harmful kinds as is necessary for nutrition.

This raises two questions :—

(1) What animal foods contain much uric acid ?

(2) How much animal food is necessary for nutrition ?

There can be very little doubt that the best answer to our first question is to be obtained by the physiological test which I have used in the case of meat (see chapter iii., and *Journal of Physiology*, vol. xv., p. 168).

That is to say, when a person is on a practically constant diet, and watching his uric acid and urea excretion from day to day, if the taking of a known quantity of some substance, such as fish or meat, always, without exception, increases the excretion of uric acid out of proportion to urea, such substance contains uric acid in proportion to the increase and should be avoided.

Such a physiological test is much more valuable than any mere estimation of the xanthin contained in meat, for what we want to know is the effect of these substances on the living human body and in so far as meat eating produced my headaches, it was, as we can now understand, the xanthins it contained which slowed the capillary circulation, raised the blood pressure and increased the excretion of uric acid in the blood and urine, and we can watch all this as the result of swallowing it.

In eggs I have been unable to find any uric acid or other members of the xanthin group, such as I have found in meat, and yet their steady and graduated administration invariably brings about a rise in the excretion of uric acid and all the evil effects of its passage through the blood, so that I have had to exclude them, from my diet.

We know, however, from the researches of others, that eggs do contain a substance which can be converted into uric acid, and that this is chiefly contained in the yolk. Therefore my results merely show that this substance was not estimated by the process I used but was rendered evident by the physiological test, which showed quite clearly that eggs do contain poison, and this physiological test is the one I always make use of when there is a doubt about any substance being uric-acid-free.

We must, therefore, take the following table as at best a rough guide to the amount of uric acid or xanthin in any food, and the ultimate appeal must always be to the effects of administration on the excretion of uric acid from day to day (see also p. 7 and figs. 73 and 75).

Substance.	Uric Acid and Xanthins. per cent.	Grains per lb.
Lamb (cold roast leg)	·050	3·5
Soup (made from bones)	·0068	0·48
,, (made from meat)	·0202	1·4
Hospital beef-tea	·0980	7·0
Saddle of mutton	·020	1·4
Mutton (cold roast leg)	·016	1·1
Veal (cutlet)	·049	3·5
Beef (cold sirloin)	·016	1·1
Kidney of sheep	·049	3·5
Liver ,, ,,	·091	6·5
Fowl (breast)	·024	1·7
Rabbit	·015	1·0
Mackerel	·032	2·2
,, (boiled only ¼ of an hour)	·015	1·0
Plaice	·0039	0·2
Herring (fresh)	·0040	0·2
,, (Loch Fyne, kippered)	·0900	6·4
,, (bloater)	·031	2·2
*Beef-steak (treated raw)	·019	1·3
*Meat-juice	·697	49·7
*Meat extract	·883	63·0
Tea	2·5	175·0
Coffee	1·0	70·0
Cocoa	·84	59·0

* These are from ch. ii., placed here for comparison.

The tissues were extracted as cooked and ready for eating, except as mentioned, and I give uric acid in grains per pound as well as in per cents., as it has been suggested to me by Dr. Rushton Parker that this would make the table more useful.

Young meat (lamb and veal) contains more than old (beef and mutton), and as we should expect, soup made from meat contains considerably more than soup made from bones. The kidney and liver of sheep contain more than their muscles, just as is the case in man, and some kinds of fish contain a considerable quantity, even more than meat; any increase in the fish taken has certainly appeared to me to markedly increase the amount of uric acid passing through the blood.

The fact that hospital beef-tea contains so much uric acid is interesting, and a pint of this beef-tea, I am informed, was made by cooking 1 lb. of meat for eight hours.

It appears, then, that this process extracts about five times as much as I have obtained from similar muscular tissue, but then I only boiled it for half an hour (see chapter xviii.). This renders it probable that I have only extracted from the tissues in the above table from a quarter to half of the uric acid they really contain; getting relatively more from the younger or softer tissues, which broke up more easily, and less from the older and tougher tissues.

As regards the animal foods, their infusions and extracts, the figures given represent uric acid plus other members of the xanthin group, and tea, coffee and cocoa contain xanthin compounds, not uric acid; but these may, for all pathological and physiological purposes, be regarded as one and the same substance, producing throughout the body and its tissues the same effects.

Then I find that a single supper or dinner of soup, fish and meat increases the urate excretion of the following three or four days by about 4 to 6 gr.; but the animal food taken at such a dinner, including soup and meat extracts, probably does not exceed the equivalent of ¾ lb. of meat, so that the results of digestion correspond fairly well with those of long cooking in the case of the above beef-tea.

It needs but a very simple calculation from the figures to show that tea is by no means the harmless substance it has been supposed to be, and that in place of causing a little dyspepsia by tanning the gastric mucous membranes, it may really bring about, in the course of a year, the introduction of a huge quantity of uric acid, and thus account for some of the most serious effects of collæmia or arthritis, of which we had probably one instance on p. 290.

I may mention, while speaking of tea, some figures kindly sent me by Dr. C. E. Lockwood, of New York, as obtained by a friend of his, Dr. W. J. Morton, while experimenting on himself with tea.

He took from 4 to 8 drachms of green tea infused in a pint of water, and continued it for seven days, and as a result uric acid rose from 5 gr. up to 8, 10, 11, and 13 gr., while urea fell steadily from 591 gr. to 422 gr. in the same time, this fall of urea illustrating the depressing effects on metabolism of excess of xanthin or uric acid in the blood (see chapter viii.).

I am glad to see that Dr. F. B. Turck points out that the injurious effects of meat are due to its extractives, with which he was able to produce distinct symptoms of poisoning and often death in dogs, mice, and rats (see the *Medical Examiner and Practitioner*, vol. xvii., August, 1907). I can answer for it as a matter of clinical observation that small children who have been given considerable quantities of meat juices and extracts occasionally die unexpectedly within a few weeks; and it was the absence of obvious cause for these deaths that led to their being observed.

How much animal food is necessary for nutrition?

I have had in my experimental work the most absolute proof that a sufficient supply of nitrogen is the prime necessity of nutrition.

For before I became aware that the uric acid which poisoned me was being poured in ready formed in flesh foods, tea, coffee, &c., I believed that the only way to reduce uric acid was to reduce total nitrogen, and this I proceeded to do, with the unfortunate result of reducing myself to a condition of extreme debility and asthenia.

But when I found out, in 1893, that all uric acid and xanthin swallowed appeared in the blood and eventually in the urine, I saw that I could take as much nitrogen as was necessary for nutrition as long as I avoided substances containing much uric acid or xanthin.

I will now show in fig. 73 an epitome of my results during four years, each dot in the curves there given corresponding to a month's excretion.

The figure begins with December, 1893, where we see urea is very low, at 10,000 gr. in the month, or 322 gr. a day, which for 125 lb. of body weight is only about 2·6 gr. per pound per day; but uric acid is high, 12·8 gr. per day, giving a relation of uric acid to urea of 1—25.

This was a condition of considerable danger, as my tissues were not only under-nourished from want of albumens, but circulation was very defective owing to collæmia; and I was thus exactly in the condition in which tubercle or any of the exanthemata, or other parasitic diseases, might have flourished in spite of a very free allowance of fat, sugar and starch. I trust that this experience of mine may act as a warning to others not to try the starvation road out of their difficulties, it being at once dangerous and unnecessary.

This is exactly the condition of the women mentioned above, who suffer from severe collæmia because unable to take sufficient food; and here is a further justification of the quantities I order.

From this onward we see a steady rise of urea till in February, 1895, it has reached about 387 gr. a day, and in June, 1896, to about 419 gr. a day. And uric acid, which was above 14·7 gr. several times in 1896, and above 13·7 in 1895, falls towards the end of this year (1895) to 11·9, and has remained about this level, its relation to urea in the early part of 1897 being very close to the supposed level of formation, 1—35.

So that at the present time the uric acid excreted in a year is nearly 500 gr. less than in 1894, and urea is nearly 30,000 gr. a year more.

The great fall in uric acid is entirely due to the gradual elimination from my diet of substances containing it or its xanthin rela-

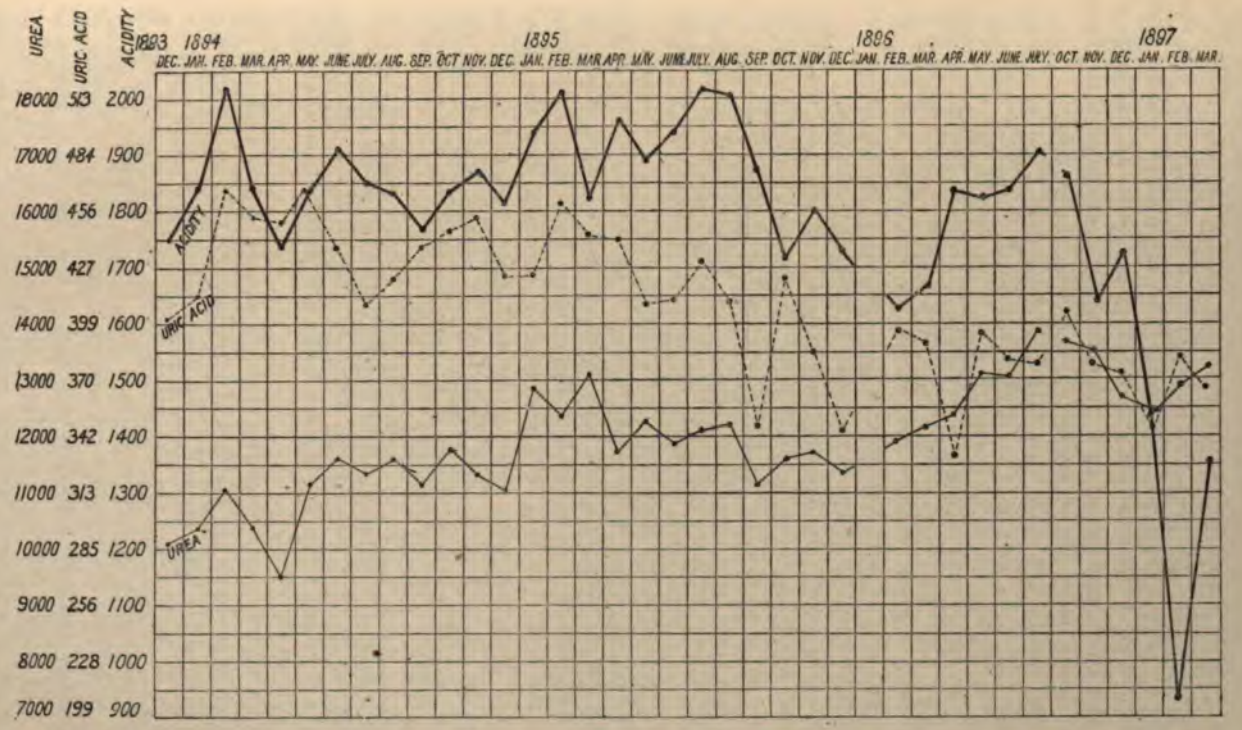

FIG. 73.—URIC ACID, UREA AND ACIDITY EXCRETIONS MONTH TO MONTH, SHOWING EFFECTS OF DIET OVER YEARS.

tives. Thus up to the early part of 1894 I was taking both fish and eggs, in 1895 I took fish perhaps once a day, at the end of 1895 I took neither fish nor eggs, and in the latter part of this year and the whole of 1896 I gradually eliminated from my diet all articles that contained even the smallest quantities of egg, such as puddings of various kinds, and cakes, as I got very distinct evidence that these when taken every day increased the excretion of uric acid.

The curves tell their own tale and show that I am now practically free from uric acid, and that the small output of this substance is not due to its small excretion or retention owing to rising acidity and urea, for in February, 1897, I took a large amount of alkali and greatly reduced the acidity of the urine, and yet the resulting rise of uric acid was small indeed, showing that there were practically no stores in the body available for solution.

I would point out that with this great fall of uric acid my blood decimal has gone up since 1894 fully 10 per cent.; that my pulse is now never so slow or my blood pressure so high as it used to be, that headache and mental depression are steadily and completely absent, while nutrition, strength, and power of endurance are better than at any time during the previous fifteen years.

It may be said that the improvement in the blood decimal is due to the rise of urea, and this is no doubt correct to some extent, for the nutrition of this circulating tissue must have improved along with the rest; but this will not explain the fact that the blood decimal fluctuates with the hourly and daily fluctuations in the excretion of uric acid, and that both in myself and others the swallowing of uric acid or any of its xanthin relatives will promptly bring it down without affecting urea at all.

My blood decimal has further improved since 1898, and is now between ·7 to ·8, which is on or above the normal of any other scale, and 15 to 20 per cent. higher than I had got before on ordinary diet (see note in chapter xii).

This figure therefore shows that the excess of uric acid and the diseases it produces are matters of introduction, that no reduction of urea compatible with life will bring down uric acid so long as introduction is continued. On the other hand, so long as uric acid is not introduced, urea may be kept at any height required by physiology to furnish the greatest amount of force the body is capable of producing; and with sufficient urea and in the absence of excess of uric acid it can furnish force for nutrition, strength and power of endurance to an extent which is greatly in excess of anything that can be done when fed on animal flesh and vegetable alkaloids; and

the rate of the capillary circulation tells us in a moment whether we have to do with an organism which is hampered by the friction causing collæmia or with one which has a free circulation, and which will consequently excel both in force production and in endurance.

My experience, therefore, leads me to answer the question of the quantity of animal food necessary for nutrition as follows :—

No animal food at all is necessary, for the whole of the required nitrogen can be got from the vegetable kingdom, but as milk and cheese appear to have no power of increasing the excretion of uric acid they may, if necessary, be used along with the vegetable foods.

As to the quantity of nitrogenous food required, my experience leads me to believe that the allowance given in most works on physiology of 3·5 gr. of urea per pound of body weight per day is very close to the mark for a healthy and active adult man.

Children may require nearly three times as much, as they have to grow as well as to keep up nutrition ; sedentary adults require less, and those who are old as well as sedentary much less.

Thus, for myself, I believe that somewhere between 3 and 3½ gr. per pound per day is the best amount of urea, near the higher limit when I am taking a considerable amount of exercise regularly, and near the lower when I am very sedentary, as in bad weather in winter.

Then as urea multiplied by three equals roughly the albumen required to produce it, if the weight is known, it is easy to calculate approximately the quantities of the various food substances that will have to be taken by any given person.

But for adults leading ordinary and somewhat sedentary lives, it suffices to multiply the pounds in the body weight by 9 ; thus, a man of 140 lbs. will require 140 × 9 = 1,260 gr. of albumen per day, and I believe it to be dangerous to go below this quantity (see *Medical Record*, August, 1905) where I have pointed out that it is not safe to take less than the quantity of albumen just mentioned).

That those who take even a fraction less, and continue to do so for twelve to eighteen or twenty-four months, come as a result to suffer from increasing anæmia, subnormal temperature, and eventually also from deficient strength and power. In a later paper on "Heart Failure as the Result of Deficient Food," *Medical Record*, May, 1906, I point out that this underfeeding, if continued for some time, may, under certain circumstances, result in more or less heart failure and collapse.

At the end of this paper I say: "In practice I give all adults who consult me 9 gr. of albumen per day for each pound of body weight, and though this is only a rough guide it is decidedly better than none. But because it is a rough guide I watch also the temperature of the body, the condition of the blood, the ratio of the capillary reflux to blood pressure, and the other circulation signs above mentioned (see also chapter v.), and I look upon these taken together as safe and certain guides to a condition of satisfactory nourishment and nutrition.

"Far be it from me to assert that there are no exceptions, and that no one can live on less than 9 gr. of albumen per pound daily; but those who do so must demonstrate that all these conditions remain normal, week after week, month after month, and year after year, or they will fail to persuade me that they are not underfeeding and courting danger."

This is, I believe, a true statement of the case, and that the above signs are the only safe guides in practice, if disaster is to be prevented.

With reference to this question of quantity, I note with great interest that Baron Takaki mentions in his lectures, published in the *Lancet*, 1906, vol. i., p. 1369, the way in which he was able to stamp out beri-beri in the Japanese Navy merely by increasing their allowance of albuminous foods. He found, in fact, that beri-beri was due to the quantity of nitrogen in the food falling below that discharged from the body, and he says: "The greater the difference in these proportions the more beri-beri occurred, and the less the difference the less."

This is, then, a most interesting instance in point in which a deficiency of albuminous food produces liability to disease, while a mere increase to a more normal ratio of albuminous food to body weight suffices to do away with the attacks of disease.

Such a calculation as the above should, however, only be used as a rough guide, as nutrition, the blood decimal, strength and power of endurance are the most certain indications of the necessary quantity and quality.

The rule, then, for an active adult is—find the body weight in pounds: if there is much adipose tissue deduct it, *i.e.*, take the weight of the individual before he began to get stout, multiply by 3·5 and the resultant by 3, and you will have the amount of albumen in grains that he will have to consume each day.

Thus a man of 140 lb. × 3·5 = 490 × 3 = 1,470 gr., the amount of albumen to be taken by him each day.

He must leave out all meat, fish, fowl, game and eggs, which contain, say, 15 to 25 per cent. of albumen, and replace them by—

Milk ..	...	...containing	3— 4	per	cent.	of albumen.
Cheese	...	... „	25—33	„	„	„
Bread	...	... „	8	„	„	„
Cereal foods		... „	5—12	„	„	„
Nuts or almonds		... „	15—25	„	„	„
Dried fruits...		... „	2— 3	„	„	„

He may also have garden vegetables, but these often contain mere fractions of a per cent. of albumen, or garden fruit, containing from 0·5 up to 1·0 or 1·5 per cent. of albumen only.

Practically, then, he will have to replace his flesh foods by bread and corn foods and a little milk and cheese, with nuts and dried fruits if he likes and can digest them ; and he should regard garden vegetables and fruits as sauces for the dry or less interesting bread and cheese.

I am sorry to see that Dr. Hall finds 3·4 gr. of purin (= uric acid and xanthin) in a pound of oatmeal (*British Medical Journal*, 1902, vol. i., p. 1462), and I am still more sorry to find that my own experiments seem to confirm his result.

With regard to this, I will only say that some xanthin is probably universal throughout the vegetable kingdom, just as some uric acid is universal throughout animal tissues ; both are products of the metabolism of life, and are probably inseparable from this,* and all we can do is to choose those things which contain least. In the same way the whole wheat grain is by no means free from xanthin, but a large part of it is removed with the germ and coverings ; hence white bread, according to Dr. Hall (previous reference), contains none ; and white bread in my experience also contains little or none. But some other breads which retain the germ and coverings contain quite appreciable quantities, and one of these which I estimated contained 2·7 gr. per lb.

This, of course, raises the question of the separation of xanthins from the other grains and the pulses, and many manufacturers claim

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* Dr. Sheridan Lea in his "Chemical Basis of the Animal Body" (p. 174) says : "The relationship of the xanthin bodies to certain vegetable alkaloids is further interesting when it is remembered that the latter are regarded by plant physiologists as waste products of the vegetable organisms, and are thus found chiefly in those parts of the plant which are on their way to removal, viz., the bark, leaves and seeds."

that they do thus remove a considerable quantity, and my results seem to show that this is true ; but I still prefer to work with cereals, which only contain from 2 gr. to 4 gr. per pound in their original condition, rather than with the pulses, which my researches show to contain as much as 16 gr. to the pound, or twice as much as most meat (muscle). But if xanthins are completely removed from the pulses then there is no more harm in taking their albumens than those of (white) bread. The ultimate appeal is, of course, to the urine and the blood ; for a man fed on meat with tea and coffee excretes some 20 gr. of uric acid a day, and has slow capillary reflux and many granules in the blood ; while another man, fed on cereals, milk, cheese, nuts and fruit, excretes only 10 gr. to 12 gr. of uric acid per day, and has quicker capillary reflux and fewer granules in the blood, albumen, nitrogen and urea being the same in both cases.

Again, there is an immense difference between taking cereals that contain 600 gr. to 800 gr. of albumens and 3 gr. to 4 gr. of xanthin per pound, and taking tea which contains practically no albumen and about 175 gr. of xanthin per pound ; here man is taking pure poison and no nourishment whatever, and with the introduction and diffusion of tea and coffee throughout the land there has come about a very great increase of all uric acid disease (see facts given further on).

With reference to tea I have the following interesting note from my friend Mr. D'Arcy Power, who says : "Have you ever read Walpole's letters ? Whenever he has an attack of gout he attributes it to tea and stops taking it."

This, then, shows that tea has not always been thought to be merely a cheering, harmless beverage.

With regard to all these cereals and the breads and puddings made from them, we must bear in mind that the outer husks of all kinds of corn contain some xanthin, and that therefore wholemeal bread, brown bread, whole meal and bran, and foods, bread and biscuits containing them, must be avoided by all those who would be as free as possible from xanthin. What you want is a flour containing the whole of the grain without any of the husk and without the germ, and this is what is commonly called best seconds flour. There is not much difference in nourishment between white bread and wholemeal bread, but the most nourishing bread of all is that made with seconds flour.

Obviously most of our fruits contain so much water that huge quantities would have to be taken to get the necessary albumen.

So our man of 140 lb. would have to take in order to get his 1,470 gr. of albumen—

14 oz. bread	(= 8	per cent.	of albumen)	—476	gr. of albumen.
2 oz. rice	(= 5	,,	,,)	— 43	,, ,,
2 pints milk	(= 3	,,	,,)	—525	,, ,,
2 oz. cheese	(=33	,,	,,)	—280	,, ,,
			Total	... 1,325	

and the remaining 145 gr. will probably be made up out of the cereal or other vegetable products he takes as puddings and out of the garden vegetables and fruits ordinarily consumed.

Now, many modifications of this diet are possible, and the best plan is for each individual to take that which suits his own taste.

For my part I regard a diet consisting chiefly of breadstuffs and cereal foods as having more advantages than any other, and this was the diet on which the athletes of Greece and Rome performed their feats. It is a diet for workers and the active, less suited for the sedentary. For practical purposes I divide breadstuffs into three classes—(1) The breads proper, (2) the biscuits, (3) the puddings and pudding stuffs; and 8 oz. of each of these three would form a large part of a day's food for anyone, and the remainder of the albumen would no doubt be made up from the fruits and vegetables taken as sauces to the breads. One pound of cereal meal alone would equal about 800 gr. to 900 gr. of albumen, and those in active work would no doubt eat from 1½ lb. to 1¾ lb. of this, and when fruit and vegetables have been added this would be a very ample diet for anyone. Those who cannot take these quantities of cereal foods can add a certain amount of milk and cheese until they can learn to take the cereals. A very large variety is to be obtained in each class of breadstuffs. The fruits cannot be kept the same from month to month, and the vegetables also necessarily vary with the season. There is thus endless variety; but these foods have been neglected till to-day they are but little known.*

The above-mentioned diet of breadstuffs, fruit and vegetables would work out into three meals a day somewhat as follows:

* To meet this difficulty practical instruction in food and feeding can be obtained at Baylis House, Slough, Bucks, a fine old mansion standing in extensive gardens and grounds. This replaces the smaller house, Apsley, which has been used for the same purpose for the past six years, being a contribution to the cause of diet reform by a grateful patient. When I enumerate to patients the foods that must be left out they often remark that there remains but little to live on, but after a visit to Apsley they are ready to admit that many of the things they have been neglecting are better than the things they have been eating, and that there is still plenty and to spare to suit all tastes.

The total for the day being, say, 24 oz. of breadstuffs and 24 oz. of fruit and vegetable, we get for each meal 8 oz. of breadstuff and 8 oz. fruit and vegetable. This will further subdivide into, say, 2 oz. of toast, 3 oz. of biscuit, 3 oz. of pudding, 2 oz. of dry fruit and 3 oz. each of vegetable and fresh fruit. Those who cannot take these quantities (and only a young adult leading an active life would require more) must take as much as they can and add some milk or cheese, or both, to make up for the breadstuffs left out, and they will gradually learn to eat more of the latter as they go on. Now, 16 oz. sounds a very large meal, but we must remember that vegetables and fruits weigh heavy and contain, even the dry ones, a large amount of water; the really solid food is the 8 oz. of breadstuffs. The best way to eat this diet is to select several kinds of breadstuffs, as toast, biscuits and pudding, and place them at one's side, and then one or two fruits and vegetables which are to serve as sauces. The breadstuffs must be weighed at first to test the amount eaten and to know how much milk and cheese have to be added, and it follows from their percentage of albumen that about 3 oz. of milk or about $\frac{1}{3}$ oz. of cheese has to be taken for each ounce of bread left out. Thus a person who falls short of his quantum of breadstuffs by 8 oz. in the day will have to add 21 oz. milk or 2 oz. cheese. Then, as a person of 140 lb. wants about 30 oz. of bread, it follows that roughly speaking a little more than 2 oz. of bread is required for a day's food for each 10 lb. of body weight. Butter or oil may be taken *ad lib.* by those who are not too stout, or in fear of becoming so, and a good way of taking them is to mix them with the vegetables. The way to take these foods is to eat the breadstuffs steadily, with an occasional mouthful only of the fruit or vegetable, which, with butter or oil, are the sauces. Or nuts can be taken by those who can digest them, and then part of the oil or butter can be got from this source, and those who can take considerable quantities of nuts or nut foods can considerably reduce their breadstuffs, as 1 oz. of nuts taken is equal to 2 oz. of breadstuffs left out. As I have said, the variety in these foods is very great, and with a little ingenuity may be made almost endless, but with this diet the taste for simple foods returns, so that it is often easy to make a meal of two, or at the most three things, say toast, potatoes and oil and dry fruit. In this way the labour of the housekeeper may be greatly reduced, and life yields more time for other things besides eating and drinking; and this without any diminution of the natural pleasure of taste and the satisfaction of hunger, which indeed are often much increased on a natural diet.

I myself make but little use of nuts, but they are very valuable foods for those who can digest them. Those who have been accustomed to eat them should certainly continue them, while those who are free from organic disease and whose teeth and digestion are sound may try small quantities of the more tender kinds and judge for themselves whether to continue them. If the result is favourable, it will be possible for these people to diminish breadstuffs by increasing nuts. As a rule men can take the quantities of breadstuffs fairly easily; it is the sedentary women who find difficulty in doing so. Thus the uric-acid-free diet is composed of foods which everyone takes, only the quantities have to be increased to replace the flesh foods left out.

Through the kindness of a friend who holds an official position in Lower Burmah I am able to give some information in regard to the diets in use in that country, and the following is the regular scheme "in force in the prisons for adult males," and the average weight for such prisoners may be taken as 120 lb., and on this diet they are said to get fat and strong.

Rice	1 lb.
Fish or lentils	4 oz.
Vegetables	10 oz.
Salt	½ oz.
Fish chutney	½ oz.
Condiments	¾ oz.

This, according to my calculations, adds up to 984 gr. of albumen, and this, divided by 120, will give 8·2 gr. per pound of body weight per day, which is a little below my standard of body weight multiplied by 9. But then these prisoners, as we may gather from the fact that they grow fat, are probably not doing hard work.

From the same source I also have a statement as to the food of the ordinary peasant in Lower Burmah, and this seems to be a long way over my standard in relation to body weight; it is said to be the full diet of an able-bodied male.

Meat	4 oz.
Fish	8 oz.
Vegetables	1 lb. 8 oz.
Rice	1 lb. 8 oz.
Fish chutney	2 oz.
Salt and condiments	1 oz.

This works out to the enormous total of 1,938 gr. per day, or,

leaving out the meat entirely, to 1,488 gr.; indeed, it seems to me that, leaving out entirely both meat and fish, the diet would still be an ample one for a man of 120 lb.

With regard to this my informant says: " . . . The Burman eats meat whenever he can get it, but I think the amount is over estimated, as many of the villagers probably never get it at all, and fish also is somewhat scarce. The bulk of the peasants live chiefly on rice and a few condiments."

So far as these statements go, there is nothing to show that the natives of Burmah are able to live on less food than I estimate for; and to be certain that even the 8·2 gr. per pound was an under estimate for weight, we must also be sure that the 120 lb. was composed of bone and muscle, and that they were carrying no fat at the time of their admission to prison.

Similar statements come to hand about the Chinese and Japanese, many of whom are reported to consume from 1½ to 2 lb. of rice per day. And for those of them who are of light weight this would go a long way to supply the albumen necessary for my 9 gr. per pound scale.

Compare with this the diet of the butcher referred to in chapter xv., who took 2 lb. of meat a day, and would get from this source alone about 2,750 gr. of albumen; from this he would form upwards of 900 gr. of urea and 26 gr. of uric acid, and as the meat introduced 14 gr. of uric acid (and if he frequently ate liver and kidney considerably more) he had daily to deal with 40 gr. of uric acid as compared with 11 gr. or 12 gr. had he been on a uric-acid-free diet and a normal allowance of albumen. He would also have a daily excretion of acid equal to about 130 gr., when 70 gr. would be enough for his weight on normal albuminous metabolism.

It is little wonder, then, that he retained large stores of uric acid from his great formation and introduction; such gluttonous feeders, given a little time, may become almost solid with urates, mere walking pillars of salt.

In comparison with such feeding, what is half a pint of milk or 1 oz. of cheese too much? It is better to take a little too much when making the change of diet than to run any danger of malnutrition with severe collæmia and collapse, and later on the quantities can be adjusted more carefully.

Constipation is an almost constant bugbear of the meat eaters, but on the above diet it is practically unknown. Those who have to take much milk and cheese may continue to suffer a little, but

as a rule it is completely absent on a diet of breadstuffs, fruit and vegetables.

Some of those who have been in the habit of eating much animal food and but little bread and starchy foods may have trouble with these latter when they begin to alter their diet.

This trouble comes chiefly in the form of discomfort, distension, or flatulent dyspepsia, and is largely due to the fact that bread and starch foods cannot be bolted, as flesh can be, with little mastication and without being mixed with saliva; bread and starch thus treated are apt to digest very slowly and may begin to ferment in the process.

The remedy is quite simple; put the bread and starch foods dry into the mouth, so that the saliva can mix with them easily, eat them slowly and chew them well.

With this object eat bread which has been cut in slices and toasted right through in the oven, or toasted biscuits; there is no objection to a little butter with them, but the breadstuffs must go dry into the mouth, not in the condition of slops or milky puddings, and no fruit or acids should be taken with them.

Another rule for those who suffer from similar dyspepsia is never to drink when not thirsty. As a rule such people can manage one and a half or two pints of milk in the day without having dyspepsia from too much fluid; but in cold weather and when sedentary even that may be too much, and the milk may have to be reduced still further, the breadstuffs and cheese being increased to replace it. An alternative way out of the starch difficulty is to live on milk, cheese and vegetables in winter, and to add fruit in the other seasons. Those who can take freely of vegetables and fruit will not require so very much milk and cheese. This diet has many advantages: there is no constipation, and the high acidity and acid dyspepsia of breadstuffs is absent, while the temporary acidity of the fruit is counteracted by the alkali in the potatoes and vegetables. (For further details see "Diet and Food," ed. vi., pp. 62 and 70).

The question of salt eating is one which requires consideration from several points of view, and I will shortly state my own experiences. On ordinary diet I used to be an ordinary taker of salt (sodium chloride), and I continued to take it for many years on a uric-acid-free diet; but I gradually found that I had less and less desire for it, and unconsciously took less as time went on. Then two or three years ago, when making some experiments on the acidity of the urine, I decided to give up salt entirely for a little and watch the results, and I found after doing this for

several weeks that whenever I took salt again I got very decided nasal catarrh, almost as if I had taken an iodide, and this has continued up to the present time, so that the moment I take a little extra salt in my food my nose begins to run. For myself I have drawn from these facts the conclusion that what is at once thrown off in this way is not wanted by Nature. I am not prepared to deny that some chloride is wanted in the body for gastric digestion and other functions, and I have seen at least one case in which dyspepsia appeared to result from leaving it off. On the other hand it seems clear that I get all the chloride I want without its being added in noticeable quantity to my foods, for as soon as salt can be tasted in my vegetables or my cheese I get symptoms of chloridism. As regards the excretion of uric acid, salt does harm, for the addition of a mineral acid raises the acidity of the urine and diminishes the alkalinity of the blood and tissue fluids, and it is no use to clothe warmly and to eat potatoes and avoid acid fruits while swallowing considerable quantities of salt. My own practice, therefore, is to take no salt except on the rare occasions that I feel a distinct desire for some; and I even go further and avoid those foods to which salt has been added in appreciable quantity (see also remarks as to the causation of cancer in chapter x.).

But while most uric acid troubles are due to introduction of uric acid formed outside the body, it is also quite possible to suffer from excess of it in the blood, if the formation in the body is excessive and if all that is there formed is not excreted.

Now, as uric acid is always formed as far as we know only in the relation to urea of 1—35, there will be no excessive formation of uric acid unless there is also excessive formation of urea, unless, in fact, more albumen is taken in than the body requires for its nutrition, or more than will form from 3 to 3·5 gr. of urea for each pound of body weight per day.

But such increased intake of albumen and excessive formation of urea and uric acid entail also increased formation of acids, and these last, by diminishing the alkalinity of the liver and the blood, bring about defective excretion of uric acid; thus excessive formation of uric acid is generally accompanied by defective elimination, and these two causes working together soon produce an accumulation in the body which eventually comes through the blood, or is driven out of it into the fibrous tissues, producing trouble (see case of butcher previously given).

Now, when 3·5 gr. of urea are produced for each pound of body weight per day, 35 gr. of urea and 1 gr. of uric acid are produced for

each 10 lb. of body weight; and if 7 gr. of urea are produced for each pound, then 70 gr. of urea and 2 gr. of uric acid are produced for every 10 lb.; and though such a rate of production as this can only very rarely be met with except in children, it is by no means uncommon to find urea 1½ gr. or even 2 gr. above the physiological level of 3½ gr. per pound.

Now, this may be done on any diet, whether animal or vegetable, and those who do it will undoubtedly very soon come to have considerable excess of uric acid in their bodies, which sooner or later will produce its usual effects.

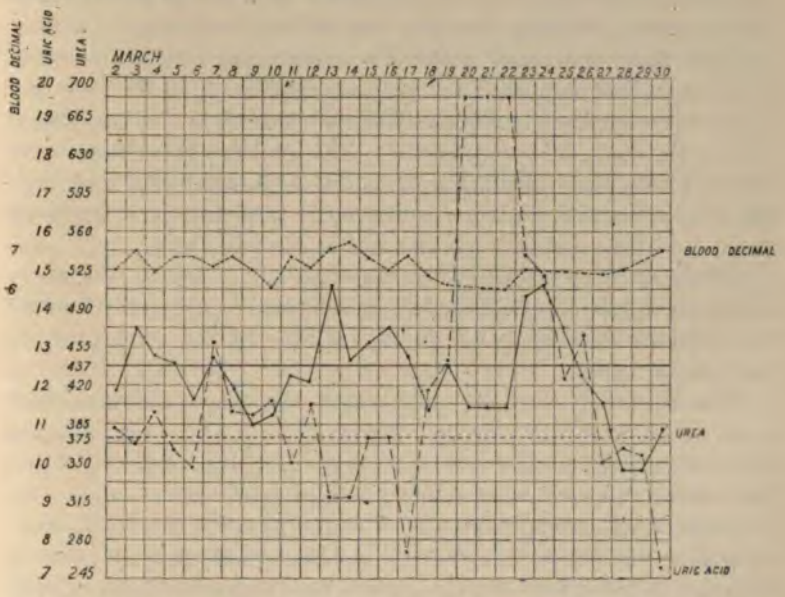

FIG. 74.—URIC ACID AND UREA EXCRETIONS AND THE BLOOD DECIMAL FROM DAY TO DAY; SHOWING THE EFFECTS OF DIET IN THE PRODUCTION OF AN ATTACK OF GOUT, AND ITS CURE BY SALICYLATES.

Now, fig. 74 shows that I have myself on some occasions taken too much albumen, and have consequently formed too much urea and too much uric acid; as a consequence of high acidity I have failed to excrete some of this uric acid, and have eventually suffered from some of the troubles it produces.

This figure also shows two lines across it—one a continuous one at the level of 437 gr. of urea, that is of 3·5 gr. per pound per day of my weight; and a broken line at the level of 375 gr. of urea, which is 3 gr. per pound per day of my body weight.

And the proper level for my urea is between these lines; if it is above them I am forming too much urea and too much uric acid, some of which I tend, especially in the cold season, to store or retain in the body; if it is below them I have less urea than is required for the best condition of nutrition, strength and power of endurance.

As regards uric acid troubles, however, it is better to be below these lines than above them; but it is best of all, and not really very difficult to attain, to keep between them.

I shall now go on to describe this figure and explain how it was I got above the lines. In this figure we have really only to regard the two curves, the unbroken line, urea, and the broken line of strokes, the uric acid; the upper dotted line, the blood decimal, is merely given because I happened to be investigating it at the time this figure was evolving, in further illustration of what I have already said on the subject in chapter xii. With perhaps one exception on March 10 the blood decimal and the uric acid always move in opposite directions, and that one exception is probably to be explained in the way I have already pointed out in reference to fig. 52.*

We see, then, on following the urea line, that it was above 437 gr. level on March 3, 4, 5, 7 and 13 to 17, and again from 23 to 25, that it was only below the 375 gr. line for two days near the end of the figure.

The uric acid curve fell most below the urea exactly at those times when urea was highest, March 2 to 6 and 11 to 18, and this means, not that the natural formation of uric acid was altered, but that its excretion was hindered and diminished.

Now, if we estimate the quantities by which uric acid fell short of urea on these days, which is easily done by adding up the number of grains included between the lines of the two curves, thus, say 8 gr. from March 2 to 6 inclusive, and 22 gr. from March 11 to 18 inclusive, we get a total of 30 gr. of uric acid thus kept back and retained in the body.

Subtract from this the quantities by which uric acid exceeded urea, namely, rather less than ½ gr. on 7th, and rather more than ½ gr. on the two days 9th and 10th, taken together, and ½ gr. on

* I may say with regard to the average height of my blood decimal, ·65 to ·7 as shown—and it has since risen above this—that the great majority of those I see suffering from uric acid diseases have a blood decimal of only ·4 or ·5, and the enormous difference that this factor alone must make as regards function, nutrition, and the power of resisting microbic diseases is obvious to all physiologists.

18th, making a total of 1½ gr. of plus excretion; and 1·5 from 30 gives us a total retention in the body of 28·5 gr.

On the 19th I had a rheumatic pharyngitis and a slight similar affection of the larynx, probably as the result of some fluctuations in acidity, because I had taken some alkali on the 17th to increase the excretion of uric acid, and this was unfortunately followed by a dinner with wine on the evening of the 18th and some exposure to cold winds.

I may say that these are very common affections with me when I have too much uric acid about; and a little exposure to cold, or fluctuation in acidity otherwise caused, then suffice to bring them on.

Their pathology, as already explained, is that of gout of the fibrous tissues in any part of the body; they are due to a collection of uric acid in those tissues, and are relieved by anything (alkalies or salicylates) which increases its solubility and removes it from the tissues.

When I have no excess of uric acid in the body, neither cold, acids, nor anything else will produce such a pharyngitis or laryngitis.

But to return to the story of fig. 74. When I felt the slight pharyngo-laryngitis I tried to get rid of it by taking more alkali, but I suppose I did not take enough to counteract the exposure to cold or the rise of acidity produced by the wines; in any case the trouble increased and I began to feel rather ill with a rising temperature.

I then decided to give up alkalies and take salicylates, as with rising temperature their action would soon be the most satisfactory. I knew, however, that this was a dangerous course, for the reasons given in chapter xvi., and that I should undoubtedly be worse when the alkalies I had taken and the salicylates I intended to take met and came into collision. But I had not at the time fully appreciated the meaning and extent of the retention shown in the early part of the figure, and still less the serious introduction in the pulses I had been taking (see fig. 75), and therefore wrongly concluded that I had but little uric acid in my body and could afford to play with it.

The result, however, was a lesson which I shall remember for years, and I hope it will instruct many people besides myself and save them from making a similar mistake.

On the evening of the 19th the salicylates and alkalies met in the blood; the alkalies were still in some force from the doses taken in the morning, and the salicylates were just coming into the blood from the doses taken later, and the result of this was that my

pharyngo-laryngeal trouble increased and extended downwards to the trachea, and there was also added a new centre of inflammation in the intestines, with severe pain in the region of the umbilicus.

With this on the 20th my temperature went up and up, first above 101° F. and then above 102° F., so that in the early part of the day I was too ill to do anything but lie in bed as quiet as my cough would allow me to remain.

Towards evening, however, the salicylates which I continued began to get the best of it. The pain in the chest and abdomen moderated, and I was able to get some sleep; but I was not even yet over my troubles, as at about 4 a.m. on the morning of the 21st I woke to find myself with again very severe pain in the chest behind the sternum and a frequent and painful cough (acute gout of the trachea and bronchi). Now the explanation of this relapse was fairly simple, for the salicylates had got the best of it on the previous evening with the rising acidity; but in the natural course of events there would be a fall of acidity in the early a.m. hours, and with this the dead point, as I have called it, between alkalies and salicylates would come once more into possession of the field (see fig. 71 and remarks on it).

I accordingly took some doses of ammonia and dilute acids, and reinforced the salicylates by repeated small doses, and in the course of an hour or two they again got the upper hand and the gout passed off.

But while the struggle lasted I was in most severe pain, and had a frequent cough feeling, as if it must tear my chest open, but with no expectoration, and I lay beyond and above my pain in no little fear of danger to life itself; for though I had had and recovered from a similar trachæo-bronchitis, I knew that I had in this case done what was very foolish, and I did not quite know how soon my drugs would relieve me or how much damage might in the meantime be done to structures of vital importance.

For if there is one thing more than another certain, it is that these acute uratic inflammations of fibrous tissues regard neither persons nor places, but tend to spread along such tissues in any and every direction, affecting with equal indifference and impartiality both vital and non-vital organs; and I was uncomfortably conscious that close to what now felt like my blazing red-hot trachea and bronchi were the fibrous tissues of my pericardium and heart.

I had not only this constant burning pain in the affected structures, but the trachea and bronchi were as sensitive to cough as though they had been pounded with a hammer. Fortunately for

me the salicylates gradually again got the upper hand, the pain moderated, the cough became loose and effectual, and the expectoration of large mouthfuls of yellow pus gave ocular evidence of the acute inflammation that had been going on.

And now occurred a repetition of a result I had several times previously seen with salicylates, which were now in possession of the blood and getting the urates into solution from the inflamed tissues, and that was an alternation or migration, so to speak, of the gout from the trachea to the intestines, and from the intestines to the trachea.

If I had too much clothing over me and kept the chest very warm, the pain would begin to return to it once more, and then if I threw off the clothes, so that there was more over the abdomen and less over the chest, the chest got better, but the pain in the abdomen tended to increase, so that I was forced to reduce clothing altogether and keep both as cool as possible, and then salicylates acted well, and I was soon comparatively free from pain.

This was obviously but a repetition of many previous experiences in myself and others as to the effects of heat in preventing the solvent action of salicylates on urates, and so preventing their relieving uratic irritation, whether called gout or rheumatism, as I have often already pointed out (see chapter xvi.).

Here we also see what I have pointed out in the previous chapters, that those who are subject to catarrh, lumbago, rheumatic or gouty arthritis, and who under ordinary conditions would probably have attacks of these things brought on by cold, will, while taking salicylates, be not only absolutely immune as regards cold, but cold will help the salicylates to cure them.

Heat, on the other hand, which, apart from drugs, would have prevented or relieved the arthritis, myalgia or catarrh, will, when used along with salicylates, not only not relieve the pains, but will make them very decidedly worse (see Dr. Cowen's case, previously mentioned).

This is a point which is not only of very great importance for those who wish to treat these conditions successfully, but it is also one of which those who hold that any of these troubles are due to microbes have got, if they can, to give a satisfactory explanation.

Any arthritis, or for that matter any inflammation that is made markedly better by salicylates and cold, and markedly worse by salicylates and heat, is undoubtedly due to uric acid; and the solubility of uric acid gives the only possible explanation of the facts.

I need not describe my convalescence at length. By the evening

of the 22nd the salicylates had complete command of the situation, the pain was all gone, and the temperature was falling to about 100° F., and next morning it was almost normal, and I was able to get up. Only a cough with considerable expectoration, becoming more fluid and less tenacious, and the passage of a considerable quantity of mucus with the first actions of the bowels, now testified to the existence of the inflammations which had raised the temperature and occasioned the pain.

It will be noted that the excretions of uric acid and urea in fig. 74 on March 20, 21 and 22 are in a straight line, and this is due to the fact that on these days I was too ill to do anything but collect the urine, and I consequently estimated the excretion of these three days at once and divided the totals by three, so that the actual excretion was not exactly as shown; probably there was a comparatively small excretion of uric acid on the 20th, while the salicylates and alkali were fighting and the temperature rising, and a much larger excretion on the 21st and 22nd, when the salicylates got full power and were removing the materies morbi, to my infinite relief, both in body and mind.

If we count the grains between the curves of urea and uric acid on these three days, we find that uric acid exceeded its normal relation to urea by 8 gr. on each of them, or 24 gr. on the three, and if we add to that 1 gr. on the 23rd we have an excretion of 25 gr. out of the 28½ gr. known to have been retained in the body—*sublatâ causâ tollitur effectus*, though no doubt, as we shall see presently, there was considerable introduction in pulses, as well as retention by high urea and acidity.

Had the salicylates been continued a day or two longer the whole might have been got out, and the fall of uric acid towards the end of the figure is only what generally occurs when salicylates are left off, and does not show that all available uric acid has been cleared out.

The rise of urea on the 23rd and 24th indicates, I think, that there was some defective formation of urea with the high uric acid on the 21st and 22nd, which was soon made up for and passed out with the improved circulation on the 23rd and 24th, just as I have shown to occur in the case of exercise when there is excess of uric acid available for solution in the blood, and also when the similarly produced defective combustion, which we call Bright's disease, is put an end to by suitable treatment (see chapter xiii.).

And now I have a story to tell as to the way in which I came to have the high urea shown in fig. 74, and how I consequently came to have both excessive formation of uric acid and its deficient excre-

tion, thus accumulating nearly 30 gr. in my body with the disastrous results recorded above.

Just as the 3rd edition of this book was in preparation there appeared a very interesting work by Dr. George S. Keith, called "Plea for a Simpler Life,"* dealing largely with diet questions, and giving an account of his lifelong experiences in the matter.

From this it appears that he had, like myself, been a sufferer from migraine, which improved very greatly when he gave up butcher's meat in favour of fish, fowl, game and eggs in small quantities.

In this book he dissents as much from the old remedies—bleeding, vomiting, purging and sweating—as from the new—stimulants, tonics, and plenty of good food and wine—and believes rather in a middle course—rest in bed, water hot or cold to drink, and little or no food till there is some appetite and power of digestion. He narrates not a few very remarkable results with this treatment in cases of cerebral hæmorrhage, dyspepsia, bronchitis, phthisis, and especially in mental diseases, which are most interesting and strongly support the results I have obtained and the suggestions I have made with reference to causation and treatment.

And in a more recent work, "Fads of an Old Physician,"† 1897, he extends his arguments and mentions more cases and more experiences, and he also compares my diet with his own, pointing out that I take more food than he does. But though this is quite true, I am younger, and do much more work in a day than he does.

He also rather seems to infer that a great part of the treatment of uric acid disease is a small quantity of food, and that when this is attended to you may take small quantities of fish, fowl and tea without harm.

I quite agree, as fig. 74 shows that excess of nitrogen and albumen from any source will eventually produce trouble, for it will produce excessive formation of uric acid as well as excessive excretion, as in this figure; but I think that where no excess of nitrogen is taken greater freedom from uric acid disease and far better physical powers will be obtained by getting that nitrogen or albumen from substances which do not already contain uric acid or xanthin; and that, though Dr. Keith's experiences of giving up meat and substituting fish and fowl have been favourable—just as my own were, for 4 gr. of introduced uric acid per day are better than 8 gr. or 10 gr.—

* Adam and Charles Black. London, 1896.

† These two books have now been republished under one cover. A. and C. Black. London, 1900.

he has evidently not had real immunity either from headache or from gout, and he would, in my opinion, have had much more immunity from both if he had obtained the nitrogen required for a physiological allowance of urea from sources which were free from the poison, and if he did this he might eat any quantity of albumen necessary for strength and nutrition without the least fear of harm.

In so far as Dr. Keith takes less than the physiological allowance of albumen he of necessity produces also less force than he might, and as he still swallows some uric acid he still further diminishes the force produced by increasing the friction in his machinery. In this way he may no doubt escape some headaches, for it takes, as we have seen, some force and power to keep up the blood pressure necessary to produce headache; but he only lives half a life when it is open to him to live a whole one; and so do all those who deliberately underfeed.

In summer, and when leading a fairly active life, I can take albumens sufficient to produce about 3½ gr. of urea for each pound of body weight per day without retaining uric acid.

But in winter, and when sedentary, it is necessary to take several precautions, otherwise retention will occur; very little, it is true, but still at the end of days and weeks it will mount up to 4 gr., 5 gr., or even 6 gr., and if anything brings all that through the blood in one day there will be very distinct alterations in the circulation curves, and with high blood pressure there will be more or less mental depression or headache.

The chief precautions to be taken with a view to avoiding such retention are:—

(1) To keep warm and not expose yourself for any length of time to cold, especially in the morning hours and up to 2 p.m.

(2) Not to eat acid fruits or vegetables or much jam or sugar, especially with breakfast.

(3) Not to take more albumens than are necessary for nutrition, and as life is sedentary less will be required than when it is active.

The reason for this is that acidity and urea rise and fall together, for with large production of urea there is also a large production of the acid products of the combustion of the phosphorus and sulphur in the albumen molecule, and uric acid will be retained by this high acidity in the liver and elsewhere, as previously explained.

Freedom from uric acid collæmia can only be attained by keeping introduction as near zero as possible, while excreting day by day all that is formed.

To take some alkali in the shape of potato is to be on the safe

side as regards excretion, and it does no harm when uric acid is low and there are no stores, and a good supply of alkali prevents stores. A meat eater cannot take alkali or keep very warm with impunity, as they flood his blood with uric acid and cause anæmia and debility. But those who do not swallow uric acid can keep warm or hot and take potato with impunity.

And I am inclined to believe that given this absolute freedom, or the nearest thing to it, when the blood is practically free from collæmia, and the tissues from irritation and stiffening, when the heart can drive the blood easily through free capillaries, and the joints, muscles and fascia work without creaking and jar—when, in a word, the friction in the machinery is reduced to its lowest point—I think there is good reason to believe that the machine will work and produce a given amount of external force on rather less albumin than it would require under the opposite conditions, for the force produced by complete combustion of a given amount of albumin is the same under all conditions; but if the internal work in the friction and resistance of the machinery is reduced, the external work or result will be greater.

In other words, I believe that when I am as free as possible from uric acid, I can perform my ordinary day's work on somewhat less albumen and urea than when I am not free; and that so long as I keep up this freedom I can get on well on the albumen which will produce 3 gr. of urea per pound of my weight per day.

And when I do this I am also, by keeping down acidity, which falls with urea, favouring the daily elimination of all the uric acid I form.

The remedy, then, for all minor uric acid troubles, when you are free from accumulations in your body, is not to eat more food but less; cut down the albumens for a little, but obviously this must be for a short time only, and not frequently repeated.

And those who are free from stores of urate can do this, while those who are full of uric acid from previous wrong diet cannot do it; in these latter fall of urea and acidity means increasing collæmia, high blood pressure, mental depression and anæmia.

In those who are free temporary diminution of albumens can do but little harm to either the blood or its circulation. There is no uric acid available, and the reduction of albumens is but a further guarantee that all their uric acid of formation is eliminated, and that there will be none available to do harm.

A meat eater cannot get warm without increasing the alkalinity of the blood and getting at once collæmia, anæmia, depression and

lethargy; but it is the uric acid that produces these results, not the warmth. Hence those who are relatively free from uric acid can keep warm, even very warm, without incurring severe collæmia, debility and anæmia. In their case warmth does good by preventing retention and removing the possibility of future collæmia. The same applies to the taking of alkali, and uric-acid-free feeders can do it with impunity; meat eaters and tea drinkers cannot. The former are bright and clear in the mornings, the latter never are, and have to take more tea to make themselves so. It follows from this that it is always a good thing to clothe warmly and a bad thing to be cold, for cold, especially in the morning hours, diminishes the excretion of uric acid and stores it in the body. But the object of all must be to introduce no uric acid, to form as little as may be, and to excrete day by day all that is formed, so as to get as free as possible from accumulation and its results.

Those who get collæmic and pale on an insufficient diet are those who are full of uric acid; those who are free from uric acid will not be able to produce so much force on an insufficient diet, but they will not become either collæmic or pale to any great extent; if they do so it is a sign that albumen and urea are much too low, and their position should be observed and tested. Then those who are pale will not improve on a uric-acid-free diet unless they take sufficient albumen.

This explains also Dr. Keith's observation that uric-acid-containing foods do less harm if you take them, and also all other foods, in small quantity, for the acidity being low the uric acid (both that formed and that introduced) passes out soon and there is less tendency to accumulation in the body.

But in passing through the blood it does harm, causing collæmia and anæmia, so that obviously those will have least through their blood who have to do with formation only, and those will have most through it who have to do with both introduction and formation.

And these latter will, work for work, require more albumen, because they have to expend more force in overcoming the friction that uric acid produces, as seen in the skin circulation, as measured in the blood pressure and heart work, and in the mental and bodily power of endurance; and the wear and tear on their tissues will also be greater.

So that while I quite appreciate Dr. Keith's position, the course he indicates is very far from that which is best, for below a certain point, probably 3 gr. of urea per pound per day, albumens cannot be reduced with impunity or for any length of time without diminish-

ing nutrition and increasing the risk of microbic invasion (tubercle, carbuncle, &c., previously mentioned).

And now I come to the causes which led me to take too much albumen, and to suffer so severely as already recorded. In "Fads of an Old Physician," Dr. Keith refers to a work on diet, by Dr. Dewey, of Meadville, Pennsylvania—"The True Science of Living";* and the chief point in this book is that temporary complete starvation till there is once more a healthy appetite is the best cure for a host of dyspepsias, debilities, depression, mental and bodily, headaches, and numerous other troubles, and that for similar less severe disturbances of nutrition the great remedy is to leave out the breakfast, so as to give the stomach a long rest of sixteen hours or more, with the object of allowing it to recuperate and accumulate secretions after the last meal of the previous day.

It seems, from internal evidence in Dr. Dewey's book, a copy of which I owe to the kindness of Dr. Keith, that his plans have been completely successful in a large number of cases, and it appears to me that his logic is unanswerable, and that in his main contentions he is perfectly right.

Having arrived at this conclusion, I proceeded forthwith to put the matter to the test of experience by placing myself on two meals a day—that is to say, I left out my breakfast, and the result was that I ate such a good lunch at 1 p.m. that it was impossible to take anything more till dinner time, 7.30 or 8 p.m., so that I reduced myself at once from four meals a day to two.

The result was exactly what Dr. Dewey describes. I felt extremely bright and well in the morning, and capable of very good work, both mental and bodily. At 1 p.m. I had keen hunger, even for dry bread; such hunger as I had not experienced for years. After lunch (breakfast) I felt a little bit dull and occasionally sleepy, and the mental work of the first hour or two after it was not as good as usual. About 5 p.m. I was very thirsty, and had to have a drink of water, but there was not the least desire for food till several hours later, though by 7.30 or 8 p.m. I was able to manage another fairly good meal; and thus my meals automatically, so to speak, reduced themselves to two.

The effect of this change of meal times was, I think, unquestionably that my stomach and intestines did better work, the girth of the abdomen diminished, probably from the absence of undigested residues and the comparative absence of flatus.

* Henry Bill Publishing Company and J. and J. Bumpus, Limited, Oxford Street, London, 1895.

The fæces diminished in bulk, and I experienced a general stimulation of nutrition and strength. The total quantity of food taken was somewhat increased, and urea and acidity went up in spite of my somewhat feeble attempts to reduce the quantities taken, and no doubt, having a good appetite at 1 p.m., I took more pulses than I should have taken on the four meals a day plan.

As a result of all this I got high urea and acidity, and excessive formation of uric acid corresponding to the excess of urea, and, as fig. 74 shows, retention of uric acid. The rest of the story has been told.

The result, then, was to leave on my mind no doubt that in Dr. Dewey's plan of two meals a day in place of four we have a most powerful stimulant to digestion and nutrition. Digestion is more perfect, just as with better appetite one would expect it to be, and nutrition is stimulated; the fire burns more brightly and combustion and absorption are more perfect.

That it led me into so great misfortune was no fault of the plan, but was due to my own folly in allowing my relatively huge appetite to fall to work on such concentrated foods as pulses, cheese and milk, which were appropriate enough for the lessened appetite of four meals a day, but contained too much nitrogen for the stimulated appetite of two meals a day.

If I had let my new appetite have its fling on less nourishing fruits, vegetables, and bread, and taken only my ordinary allowance of milk and cheese, all would have been well, and fig. 74 would never have been evolved or published, and I should have escaped much pain; but it is through these things we learn, and I have learned a very great deal from this lesson in diet.

First of all I have learned exactly how two meals a day cures dyspepsia, and the headaches, mental depression, &c., dependent upon it.

My verdict is that the dyspepsia is cured, just as Dr. Dewey says, by resting the stomach and enabling it to do much better work, and that it is prepared to do this is shown by the presence of the keen hunger, otherwise quite unknown. I certainly had not experienced such dry bread hunger, as I call it, for years. If anything will demonstrate the folly of stuffing a dyspeptic stomach with fresh food every three hours, an experience of this kind ought to do it. Then the cure of the headaches, depression, &c., is the simple result of the stimulus to digestion and nutrition, for acidity and urea rise and the blood is promptly (as my case showed only too effectually) cleared of uric acid, and this no doubt is still more marked in Dr. Dewey's

patients, as they are given animal flesh in any quantity and in any form they like. With such stimulation it would be quite impossible for any uric acid to get into the blood and remain there; hence headache and mental depression vanish and remain absent as long as the stimulation lasts.

But these patients, while thus taking meat, are introducing uric acid in their food, as well as forming it in their body in excess, and they are retaining it in large quantities from both sources; and if at any time the stimulation of two meals a day falls through—if any accident or shock depresses them beyond the power of two meals to revive them—then I do not envy them the result that must ensue from all the store of uric acid they are thus accumulating.

I should mention that it was no doubt partly because I gave up or became irregular with my two meals a day about March 17 and 18 (fig. 74) that I got the uric acid through my blood and suffered from the gout and other troubles; but my experience shows that my uric acid was not destroyed or burnt up by the improved nutrition, but was merely retained in the body ready to get into the blood when the conditions were favourable for this.

While, therefore, I quite appreciate the value of Dr. Dewey's plan of two meals a day as regards the treatment of gastric feebleness, debility and dyspepsia, that plan does not in any way prevent the evil effects of uric acid on the body and blood; but, acting as a stimulant to nutrition, it keeps the blood clear so long as the stimulation lasts. But if this plan is used in combination with a uric-acid-free diet, and if proper precautions are taken to avoid the consumption of excess of albumen in the unaccustomed pleasure of satifying a keen appetite, one may obtain freedom from uric acid both for the present and for the future, in that there is neither excessive formation nor unnecessary introduction nor retention, and this without sacrificing any of the advantages arising from the stimulus to digestion and nutrition of two meals a day in place of four.

As a result of these experiences in my own person, I now make use of Dr. Dewey's plan for those of my patients who suffer from dyspepsia and deficient appetite, and would thus be in an unfavourable condition for beginning a uric-acid-free diet. Such a case cannot take milk, has dyspepsia from cheese, and terrible wind and pain after the smallest quantity of pudding; but after a few weeks on ordinary diet, with only two meals a day, appetite is much better and digestion is so vigorous that the above foods can often be freely taken and painlessly digested.

It is a good rule to eat slowly, for man does not live by what he eats, but only by what he digests. Thus vegetable food, if not well chewed and mixed with saliva, or if taken in a sloppy condition with too much fluid, ferments instead of digesting, and again if so much is taken as to distend the stomach digestion may be brought to a stand, and fermentation and putrefaction may take its place. In both these ways, then, eating slowly will do good and prevent harm, and it is quite possible for a man to be better nourished on a little food eaten slowly than on a great deal eaten quickly. I have also seen several cases where people appeared to be under-nourished on my uric-acid-free diet taken in four meals or more in the day; but when the same foods and the same quantities have been taken in three meals a day, or sometimes, better still, in two, they have with better appetite done better digestive work, have absorbed more of it into their blood and passed less of it through them undigested, and consequently have been much better nourished. It is quite possible also to be under-nourished from the above causes when the quantities of albumens swallowed are considerably in excess of those required for body weight. These people may starve and die, as Dr. Dewey (previous reference) shows, not from want of food, but from digestion being constantly overpowered by its excess. Again, a diet which consists so largely of vegetable products will keep the blood well supplied with alkalies, and so all the uric acid which is formed will remain in solution and be excreted, and there will be no storage or accumulation in the body; and not only will there be no storage, but the stores and accumulations laid down on the preceding ordinary diet will be gradually got into solution and passed out of the body (cure of rheumatism and gout).

In all these ways, then, we shall get the uric acid in the body and blood under our control, and so long as we keep up this control we shall find that we have prevented the diseases which are due to its presence in excess, and this is the real and ultimate test of the truth or falsehood of all that I have said on the subject.

It will have been noted that I have left out all pulses (peas, beans and lentils) in the diet table given above, and I have now a story to tell with regard to the reasons for this.

As a matter of fact, I have never been in the habit of taking pulses regularly or in large quantity, but in the autumn of 1898 I began by mere accident, as it were, to have pulse soup regularly two or three or even four times in a week.

As usual I was estimating my excretion every day throughout that autumn, and I could not help noticing that the uric acid was often high and the excess of excretion over formation considerable.

At first I attributed this to some storage or retention from possible over-eating during my autumn holiday, when, of course, I was not measuring food accurately or observing my excretion.

But as the excessive excretion went on and on, being 80 gr. to 90 gr. and 100 gr., I had to give up this idea, for nothing I could possibly have retained in my holiday would suffice to account for it.

Then I got ill, getting rather severe lumbago and having to take salicylate to cure it; and with this, again, I got an enormous excretion of uric acid, so that excretion was in excess of formation (*i.e.*, relation to urea of 1—35) by as much as 140 gr.

By this time I had begun to suspect introduction, but in what? My diet was entirely vegetable, except milk and cheese. I was obliged to suspect something, and among other things I began to suspect the pulses.

I had now got into January, 1899, and in order to watch for introduction more carefully I lowered the acidity by increasing my potatoes, so that any introduction should at once show in excretion.

After keeping this on for some six to eight days, I found well-marked rises of uric acid on three of these days, and on then sending to the cook to enquire which days we had had pulse soup, I found to my astonishment that each rise corresponded exactly with a pulse soup day.

I had now got a definite clue and was not long in following it out. It was a simple matter to alter my dose of pulse soup to one half on the one hand and to double it on the other, and with each alteration there was a corresponding change in the excretion of the uric acid in the urine.

I now shut off the pulses entirely and put myself on salicylates to clear out, again getting enormous excretions, so that by February 17, 1899, from the middle of October, 1898, uric acid had exceeded its normal relation to urea by something over 300 gr.

To state this more exactly, I had found an excessive excretion of 308 gr. of uric acid in 126 days, during which I had had pulse soup about four times a week, or on seventy-two days, which gave about 4 gr. of uric acid for each helping of soup, and each corresponded apparently to 4 oz. of pulse.

So that pulse contained about 1 gr. of uric acid or xanthin to the ounce—about 0·23 per cent.

I then made some careful experiments with weighed quantities of pulses, and the results of one of these I now give in fig. 75.

This shows that 4 oz. of lentils taken at lunch on August 19 produced an excretion of uric acid on the 20th equal to 2½ gr. above its normal relation to urea.

So that if all the above uric acid came from xanthin in the lentils, these lentils contained 0·62 gr. to the oz., or 0·14 per cent.

It must be remembered that the pulses I took in the previously mentioned 126 days were not all lentils; but some days they were peas and others haricot beans, and in my other experiments with weighed quantities I got excretions working out somewhere between 0·11 and 0·20 per cent.

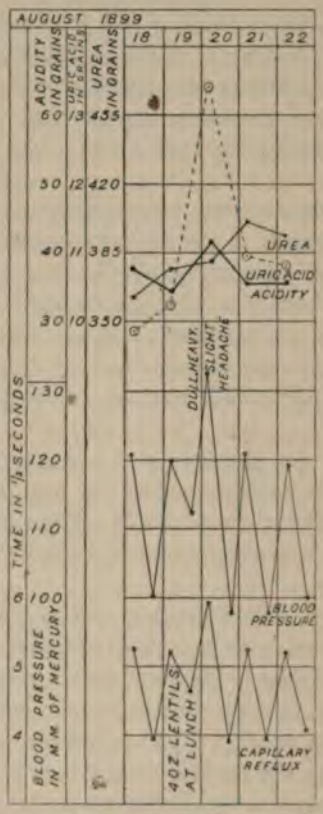

FIG. 75.—EXCRETION OF URIC ACID AFTER FOUR OUNCES OF LENTILS. EFFECTS ON THE CURVES OF BLOOD PRESSURE AND CAPILLARY REFLUX OF ITS PASSAGE THROUGH THE BLOOD.

So that I am positively certain that the pulses contain xanthin to the extent of 0·1 to 0·2 per cent., and that at least two-thirds of the above 308 gr. of uric acid came from them, if not the whole of it.

The rest of the figure shows the effects produced by the 2½ gr. of uric acid as it passed through the blood, the upper curve being

that of blood pressure and the lower that of the capillary reflux, which we may compare with the similarly produced curves in figs. 38—43.

These show that on the evening of the 19th, the pulses having been taken at lunch time, the blood pressure did not fall to its usual low evening level, and the capillary reflux was not as fast as at 10 p.m. on other evenings.

About 8 a.m. on the morning of the 20th, the blood pressure rose a little above 130 and there was a feeling of dulness and a threatening headache, and the capillary reflux was slower than on other mornings at the same hour.

Here the increased excretion of uric acid could have been told quite well from the capillary reflux or the blood pressure, and the feelings of dulness, heaviness and threatening of headache were also distinctive.

I have many similar curves produced by taking uric acid or xanthin in one form or another; but it must not be imagined that every time 2½ gr. of uric acid in excess passes through the blood it affects the circulation curves as it does in this figure.

Here it just happened that the excess was passing through the blood about the time of the evening observation on 19th and the morning observation on 20th; but when recently I was testing the amount of uric acid or xanthin in a meat extract I produced a very similar rise in the excretion curve to that in fig. 75; but this did not show at all in the blood pressure and capillary reflux curves, because the excess passed through the blood between the morning and evening observations.

But I knew when it did pass, for there was dulness and heaviness which were quite distinct, and the capillary reflux was then found to be slowed and the blood pressure raised.

This fig. 75 shows that it is a perfectly easy and simple matter to test the amount of uric acid or xanthin that any given food substance contains; but I must again caution anyone who wishes to repeat these experiments that they must not forget to keep acidity low, or the uric acid administered will be retained and not excreted.

In fig. 75 acidity is only equal to about 35 gr. of oxalic acid in the day, and bears a relation to urea, as we see, of about 1—10, and to make perfectly certain of free excretion of uric acid or xanthin swallowed I would recommend a relation of acidity to urea of from 1—15 to 1—10, the acidity being kept down with potatoes or alkaline salts of potash or soda.

We see also that by watching the capillary reflux even morning and evening we may get some fairly clear evidence of what is going on, and that by making observations every two hours we may be able to tell from this circulation curve alone whether a given food increases the uric acid in the blood and the number of hours during which the increased excretion lasts.

And from this circulation curve alone, which only takes a moment to do morning and evening, I have been able to form at least some idea of what my uric acid excretion was doing during my summer holidays, when I have no chance of collecting the urine; and I can see in these curves quite clearly the effects of exercise in increasing the excretion and causing temporary collæmia of slight fatigue, and the effects of acid fruits in quickening the capillary reflux at night, or of cold in slowing it next morning.

In the above record with the pulse foods we see very clearly the effects that continued introduction produced on me, how I got gradually worse and worse, how some was excreted but some retained in my tissues, producing among other things severe lumbago; how I was obliged to take salicylates to get relief, and how these produced large excretions and upset my digestion and appetite and powers of work as the excess passed through my blood into the urine.

Had I suspected the pulses sooner it might have saved me a great deal, and I am sorry to say that some of my patients, especially those who were stout, and had therefore been advised to take pulses freely, suffered more than I did, some of them even giving up the diet entirely.

And we need not be very much surprised at this now we see that while ordinary meat (muscle) only contains about 0·1 per cent., pulses may contain from 0·1 to 0·2 per cent., or some of them nearly twice as much as meat.

Since I found this out in the spring of 1899 I have cautioned all I could not to eat the pulses, but among those who are being treated on my lines by others, I fear some are still suffering, and that some failures to cure the uric acid headache and other collæmic or arthritic troubles have been due to this cause.

Lastly, this record shows that some of my sufferings in fig. 74 were due to introduction by pulses, and were not all due to retention by high urea and acidity; but even with the greatest possible freedom from introduction of uric acid, high urea and acidity will produce some retention, especially if aided by cold weather and acid fruits, &c., &c., at breakfast, and this will also eventually suffice to produce all the evil effects recorded in reference to fig. 74.

Then this record of the pulses will, as we shall see presently, throw quite a new light on the diseases of India: a light which is not only new, but one full of hope and promise—of promise that true knowledge will give us real power to relieve and prevent the sufferings of our fellow-subjects.

For if they are suffering, not as I had previously supposed from retention of uric acid, but mainly from introduction, that introduction can, just as in this country, be prevented, and some at least of their many deadly diseases can be mitigated or relieved.

I have also shown in a paper on "The Human Body as an Analytical Laboratory," published in the *British Medical Journal*, 1901, vol. ii., that asparagus, like the pulses, contains a considerable quantity of a xanthin body. I was led to this discovery by finding that in the asparagus season I got changes in my curves of capillary reflux, pains in my joints, and eventually more or less catarrh, which had to be treated very much as in the case of the pulses; and my other records showed that on eating definite quantities of asparagus I got results very similar to those in fig. 75, and I drew from these the conclusion that the growing tops of the asparagus contain the equivalent of 1·2 or 1·3 gr. of uric acid to the ounce.

I have had somewhat similar experiences with mushrooms, and more recently with various kinds of brown and wholemeal bread, so that I now leave out of my food all mushrooms and all breadstuffs containing the outer husk, which, as mentioned above, contains some xanthin; and once any food is suspected it is easy to put it to a similar test.

A patient sends me the following interesting note on her experiences: "I had a practical experience of that not long ago, when staying with some friends, who kindly prepared vegetarian meals for me. At the first dinner there were pulses in many forms, asparagus, and so on, and not liking to decline when so much trouble had been taken, I was obliged to eat them. Next day I was in a thoroughly poisoned state, sickness, cold hands and feet, and headache, which carried me back to the days before I began the diet."

This patient being uric-acid-free, the introduced uric acid passed into solution at once, causing immediate collæmia.

Another patient sends me a note of interest in this connection. She says: "In Marion Crawford's charming book, 'The Rulers of the South,' I find the following: 'The Pythagorean Brotherhood abstained from eating flesh, as most mystics have done, but they were as careful never to eat beans.'"

With reference to the bad effects of returning to poisonous foods,

some very interesting experiments on rats have recently been published by Dr. Chalmers Watson in the *Lancet*, 1906, vol. ii., p. 145. Among his results he found that an exclusive meat diet produced a high mortality in rats in early life, and also tended to cause scanty hair, dry skin and more or less general marasmus; it tended to hinder reproduction and to diminish the power of lactation, and many animals thus fed succumbed to diseases at an unusually early age. Whether we may rightly argue from rats to men in this manner I cannot say, but we have seen in previous pages that giving up meat diminishes the pain and suffering of child-bearing, and increases power of lactation.

Several years ago (*British Medical Journal*, 1888, vol. ii., pp. 10 and 11) I pointed out that Sir A. Garrod had fallen into an error of some importance in his argument regarding the results in a table which he quotes from Lehmann.

From this table it may be seen that the uric acid-urea relation on a

Mixed diet is ... 1—29.
Animal diet ... 1—38.
Vegetable diet... 1—22.

and Sir A. Garrod draws from this the inference that uric acid is not so much influenced by the nature of the food as urea is, and, further, that animal diet does not increase the formation of urate, but rather the reverse, while a vegetable diet does increase it.

But these results refer only to short periods of time. They refer, therefore, to excretion merely, and tell us nothing whatever about formation and introduction.

Undoubtedly the first effect of animal diet, as of uric acid itself, is to diminish the excretion of uric acid because it raises the acidity of the urine and diminishes the alkalinity of the liver and blood, and conversely a vegetable diet increases the excretion of urate because it lowers acidity; but if these investigations had been continued for weeks and months straight on, it would have been seen that the diminished excretion on animal diet would have been balanced later by a plus excretion of more than the equivalent amount, and the plus excretion on vegetable diet would gradually have fallen towards the level of formation, 1—35, when all previous accumulations had been removed.

As a matter of fact, formation never varied in relation to urea one jot, being the whole time at or about 1—35 or 1—40, only on animal diet part of the urate formed and introduced failed to be excreted and was kept back and retained in the body, while on the vegetable diet

some little urate previously formed obtained enough solvent alkali to effect its solution and excretion.

The figures are, I doubt not, perfectly correct, and agree in every way with my own results; they refer, however, only to short periods of time, and owing to the prevailing idea of excessive formation of urate, the conclusions drawn from them are, I believe, erroneous in the extreme (see also chapter iii.).

Liebermeister ("Vorlesungen über Specielle Pathologie u. Therapie," vol. iii., p. 42) falls into similar error, as he says (my translation): "In early times it used to be thought that in gout one ought to limit the use of proteid substances as much as possible in order to put a stop to the excessive formation of uric acid. One forgot, however, in taking this simple view of the matter, that it is not of much consequence how much nitrogenous material is oxidised, but only whether it is more or less completely oxidised"; and he goes on to say a healthy man excretes so much urea and so much uric acid in twenty-four hours, but an increased consumption of proteids increases to a corresponding extent the urea, but not the uric acid.

That is to say, he infers that because the *excretion* of urate is not increased by a meat diet, relatively less urate is formed, or, as he would probably put it, it is further oxidised into urea and got rid of.

The real fact is, I believe, that urate is *formed* in proportion to urea just as on any other diet, and animal food also introduces some urate ready formed, but excretion falls short of formation and introduction owing to rising acidity, and some part of that formed and introduced is held back in the body and can be washed out and produced at any future time by administering a dose of salicylate, alkali, or other solvent (see fig. 74); or, if the curves of excretion are watched sufficiently long, it may come out of itself when from some natural cause the acidity falls; or, given to a person, like the above-mentioned patient, whose blood was in a condition to dissolve it, introduction would show at once in an increased excretion.

I think, therefore, that once for all we may free our minds from this bugbear of formation, oxidation and other more or less theoretical myths, and believe that for all practical purposes uric acid is always, and on all diets, formed in the relation to urea of about 1—35, while certain foods also introduce a more or less important quantity of uric acid or xanthin ready formed (for some interesting results obtained by administering hypoxanthin to animals, see Lea, "Chemical Basis of the Animal Body," p. 182, and compare this with my remarks in chapter iii.).

I am interested to see in this connection that a writer in the

Journal of Physiology (vol. xxii., p. 146), W. J. S. Jerome, gives as one of his conclusions, after an investigation of the subject, that the daily output of uric acid is probably due to the larger or smaller amount of the alloxur-holding bodies (*i.e.*, xanthins) absorbed from the food, this conclusion being identical with that I have drawn from my own researches published in the same journal, vol. xv.

See also the *New York Medical Journal*, 1896, vol. ii., p. 578, for the record of toxic symptoms produced in a rabbit by the administration of hypoxanthin in the food; I have often produced some symptoms in myself, and I have not the least doubt that I could reproduce them in anyone who would volunteer a *corpus vile* for the purpose.

Oxidation is no doubt important, and oxygen is occasionally useful, and I have consumed a quantity of it experimentally. When I managed to raise the acidity of the urine and diminish the alkalinity of the blood, I cleared that fluid of uric acid and no doubt improved nutrition, combustion and metabolism; but it is not nearly so powerful in this way as a few fractions of a grain of mercury or one of its salts. And I do not for a moment believe that all the oxygen and oxidation in the world will alter in the least the relative formation of uric acid and urea in the human body. The diseases from which we suffer have far more to do with introduction than formation.

Whether uric acid will be excreted in the relation 1—35 is a different question, for excretion can be varied at pleasure in almost any direction and within very considerable limits. And it is by taking excretion as proof of formation that the authors above quoted have fallen, as I believe, into error. I do not assert that uric acid is never formed in excess of the relation to urea of 1—35; my experience is too small to carry such a proposition; but I do assert, of the diseases of which I have written, in so far as they are due to uric acid, that they are due to its accumulation in the body from introduction combined with failure of excretion; that I have never met with evidence of formation in excess of the above ratio to urea, or any reason to think that all the urate I have met with could not have been easily accounted for by failure of excretion.

For my part, I return without hesitation to the doctrine of early times and fight uric acid disease by reducing the introduction of uric acid and, where necessary, its formation also, believing that the clinical observation of Cullen, "that gout seldom attacked persons employed in constant bodily labour, or those who live much upon vegetable diet," is a more valuable guide in treatment than many

more recent conclusions founded on imperfect observation. We now know that constant bodily labour facilitates excretion (figs. 46 and 47), while vegetable diet both diminishes introduction and facilitates excretion.

I have now also the best of all proofs of the correctness of my reasoning in practically complete immunity from a disorder which formerly threatened to interfere seriously with my work and even to cripple and shorten my life.

Such a result must speak for itself, even if the theory on which its explanation is founded is destined eventually to give place to a better one, the product of still wider knowledge.

The late Professor Humphry says (*British Medical Journal*, 1888, vol. i., p. 512) that 62 per cent. of the aged take but little animal flesh, and I should link this with Cullen's observations and the very deadly effects of many of the diseases mentioned in previous chapters.

In altering diet, however, it is necessary to exercise some care, especially in regard to the amount of urate that may be stored in the body. In a man of middle age or beyond it, who has lived heartily, without stinting either meat or wine, there is sure to be a large collection of urate in the body; and if his animal food is reduced and his acidity runs down, this will be dissolved out and flood his blood; for weeks and months there may be a plus excretion of urate, and its results will be more evident than pleasant; he will worry you with continual complaints that he is getting weak, that he is dying, that he has headache, depression, &c., and may even talk of suicide. Similarly, in cases which have been put on what I regard as the most dangerous of diet cures, that of meat and hot water, it is wiser to go slowly and get them back gradually on to ordinary flesh diet, and then from that on to a uric-acid-free diet; but to make a sudden change on to this latter at once may bring about severe collæmia, with high blood pressure and all its most serious results, especially in those who are no longer young. In all cases, also, it is necessary to see that nutrition, strength and power of endurance are quite as good on the new diet as on the old; in the majority of cases they are decidedly better on the new; but if there is the slightest suspicion of their not being so, some mistake is being made, or a great flood of uric acid is putting out the fires, and the matter should be investigated. In other cases, where the accumulations are not so large, one may gain so much by stopping the large daily introduction that it is better to alter diet at once, especially to cut off soups, meat extracts, strong tea or coffee, giving perhaps cold

baths, a tonic or some drug which will cause a little retention and keep the blood moderately clear of uric acid for a little; or, if the diet alteration is being made in spring or summer, the patient may be sent for a few months to a bracing climate; and lastly, some cases with high blood pressure may be best treated just as if they were Bright's disease (see chapter xiii.).

As I have said before (see *Practitioner*, April, 1891, p. 279), I believe that the great majority of Britons of the present day could live very healthy and hearty lives on such a diet as I recommend if they would make a rational attempt to do so.

They think the diet must be lowering, and believe that beef steaks and beer are necessary for their continued existence, and undoubtedly, where the change of diet is allowed to produce considerable collæmia, the resulting mental depression, with languor and disinclination for excretion, are sufficient to give some support to their assertions.

But such results are unnecessary; they are not due to the new diet, but to the amount of urate which has been accumulated on the old one, and to the fact that these people have become accustomed to a stimulating diet, just as they might have become accustomed to an allowance of alcohol; but few people would in these days argue that alcohol is either a necessary food or a source of strength, though this was firmly believed not long ago.

Another objection sometimes urged against the diet is that people tend to grow stout on it, and no doubt if they eat large quantities of butter, fried vegetables, cream and cream cheese, and drink much milk, this may be the case; but this is not a necessary part of the diet by any means; for milk may be skimmed or left out entirely; if, as in other countries, bread, rice or macaroni form the staff of life, butter and cream may be avoided, and skim-milk cheese may be eaten in place of cream-containing cheese.

Where cases of obesity have very high blood pressure and slow capillary reflux, where in fact the obesity is, as I expect it generally is, a result of defective circulation and its resultant defective combustion, in a word, a result of collæmia, they should, I think, be treated just like the cases of Bright's disease in chapter xiii., where we saw that a case that did well steadily lost weight as the circulation quickened and the temperature rose and the albumin diminished; while a case that did not do well, in which the temperature did not rise or the albumin diminish, steadily gained weight.

These cases will lose weight as the circulation quickens and the combustion improves, in spite of a uric-acid-free diet, though the

fats should as far as possible be removed from it by substituting protene, plasmon or gluten for milk; or let them go on to a diet of bread, fruit and nuts, which practically does not fatten anyone.

When obesity is treated as a failure of combustion it will be treated with success; but to treat it on a pure meat diet is to obtain temporary success perhaps, but only with the certainty of a great increase of collæmia, and diminished combustion at some future time; and all the necessary albumens can easily be obtained from the above substances without introducing uric acid, and without the terrible sameness of food which disgusts those attempting a meat diet.

Obesity has, from this point of view, many features of interest, for women get stout first of all just in the period of collæmia and anæmia that follows their years of greatest growth (13 to 14), about which I have spoken in reference to the causation of anæmia (see fig. 59). So that here again we have failure of combustion with collæmia.

Then the great time for obesity, both in men and women, is the decline of life, the collæmia of advancing age, as nutrition begins to run down and the uric acid stored in previous years re-enters the blood, and then we may get not merely defective combustion of fats but defective combustion of albumen and sugar, either together or one after the other, but all associated with the same signs in the circulation, slow capillary reflux, and high blood pressure (see chapter v.).

Thus slow capillary circulation is the cause of the defective combustion, and collæmia is the cause of the defective circulation.

In butchers we often see much obesity, because there is much collæmia; and this alone should warn us not to treat obesity by a butcher's diet.

Nor must we forget that collæmia means defective pulmonary circulation (see chapter ix.), and so defective aeration of the blood; then defective oxidation means defective formation of acid products of combustion, defective acidity of urine and increased alkalinity of blood; and increased alkalinity of the blood in its turn increases collæmia, and so on in a vicious circle with ever-increasing defect in combustion. Later the obesity, by its very mass, becomes a direct hindrance to circulation, respiration and metabolism. If we can stop the collæmia even for a week we can stop the downward progress and substitute an increasing metabolism for a diminishing one, and then all is soon well, the fire burns up brightly, and this of itself suffices to prevent collæmia. And so intimate is the relation-

ship between obesity and collæmia that practically every relapse of collæmia is accompanied by an increase in weight, just as the relief of collæmia, and still more the relief of the severe collæmia of Bright's disease, is accompanied by a loss of weight.

But as there are plenty of people walking about and imagining themselves strong when they are not so (*e.g.*, stout people with slow capillary circulation, high blood pressure and dilated or fatty hearts) all who propose to alter their diet should be carefully examined, and those who are stout or otherwise weak should make the change very slowly, great care being exercised that the quantity of albumen shall not be deficient.

Stout patients who are debilitated must on no account be allowed to diminish albumens in the hope of getting thin, indeed, they should not entirely give up meat till it has been proved that they can take enough uric-acid-free albumen to be well nourished.

Much can be done for such stout people by cutting down fluids, avoiding cream, butter, fat, and fried dishes, replacing vegetables by a little fruit, and always taking sufficient albumen, while avoiding entirely the unnecessary xanthins in the coffee and meat soups.

It is possible to reduce weight fairly quickly (2 to 3 lbs. per week) on a diet of biscuits and fruit, and as far as possible no other food or drink, except water when thirst is great.

This treatment should generally be reserved for those who are free from serious organic disease, should be carried out under strict supervision and only for a limited time.

Some interesting points with regard to the possible effects of diet are brought out in the Reports of the Sanitary Commissioner with the Government of India, and I owe these facts to my friend, Dr. de Watteville, who kindly suggested that it might be worth while to investigate these Reports.

The following figures are from the Annual Report for 1892, issued in Calcutta in 1894, and they refer to the incidence of the diseases mentioned in the English and native armies respectively.

The English army numbered, according to the Report, 68,162, and the native army 145,340, and the ratio of English to native is about as 1 to 2·1.

My cousin, Colonel P. de H. Haig, I.M.S., informs me that the English army in India eats as much meat in a day as the Indian native army does in a week, man for man ; that the native army lives chiefly on grain and rice, that they have a long service system, not short as for the English, and that the natives have been exposed to malaria from childhood.

Disease.	69,162 English.	145,340 Native.	Ratio, Eng. to Native.
Alcoholism	273 ..	11 ..	54 to 1
Rheumatic Fever ..	115 ..	48 ..	5 ,, 1
Gout	13 ..	9 ..	3 ,, 1
Megrim	7 ..	57 ..	1 ,, 4
Epilepsy	73 ..	63 ..	2 ,, 1
Melancholia	61 ..	22 ..	6 ,, 1
Syncope	6 ..	3 ..	4 ,, 1
Dyspepsia	1,037 ..	454 ..	4 ,, 1
Typhlitis	32 ..	16 ..	4 ,, 1
Colic	311 ..	51 ..	12 ,, 1
Piles	452 ..	196 ..	4 ,, 1
Congestion of Liver ..	660 ..	117 ..	12 ,, 1
Ague Spleen	46 ..	1,405 ..	1 ,, 14
Bright's disease (all forms)	51 ..	40	(nearly) 3 ,, 1
Suicides	25 ..	9 ..	6 ,, 1
Ague	28,842 ..	65,944 ..	1 ,, 1
Anæmia	209 ..	909 ..	1 ,, 2
Bronchitis	1,925 ..	4,234 ..	1 ,, 1

Now we see that in the case of almost every disease treated of in this book, there is a more or less large excess of incidence on the meat-eating English as compared with the rice and grain-eating native.

The ratio of alcoholism is enormous, but probably factors of race and religion come in here as well as diet; but in any case it is not a record of which we need be proud.

Rheumatic fever and gout are fairly prominent, epilepsy is 2—1, while melancholia shows much greater excess; and probably the exposure of the English to heat from which they have not been accustomed to protect themselves will account for this, but none the less it powerfully endorses chapter viii.

Syncope again, 4—1, and yet we are accustomed to look upon the Englishman as strong in his beef eating, and the native as thin and weak.

Dyspepsia 4—1, and yet the English are, I suppose, younger men than the natives, and dyspepsia, as a whole, tends to increase with age.

One cannot but be struck also with the enormous incidence of dyspepsia in girls just at the age when as I have shown (fig. 59) they have most collæmia, and the comparative absence of similar troubles in boys; then again on ordinary diet dyspepsia increases in both sexes after middle life, and so does collæmia.

Typhlitis and colic are again remarkable records in relation to chapter x.

Piles and congestion of the liver tell the same tale, though no doubt they are in part related to the large alcohol record above.

Ague spleen is related to the long exposure of the native army, and is also connected with migraine above, and anæmia further on; the last-named being no doubt specially related to the large fluctuations in urate excretion, which recurrent malaria with enlarged spleen will occasion.

Bright's disease and suicide, again, represent the effects of capillaries obstructed by uric acid, and show a great excess among the English meat eaters; and for suicide we may notice that the ratio is the same as that for melancholia.

Lastly, bronchitis is nearly the same for both; but inasmuch as the native army is composed of longer service, and, therefore, older men than the English, and as bronchitis generally increases with age, it is relatively less in the native than in the English army. I have no doubt that in such a record other factors besides diet will have to be allowed for, but is is very unlikely that any of these will account for the great differences in disease incidence all along the line, and I commend these facts to the careful consideration of those who believe that the Englishman's beef is the source of his health, strength, and powers of endurance, or his superiority over other races; it is at least clear that he has no superiority over them in the matter of disease incidence, and this is an important factor in efficiency.

No doubt the native record would be still better, both as to malaria and many other diseases in these records, if they lived on grain and avoided pulses entirely.

I am indebted to my friend, Dr. E. G. Horder, who has spent a good many years in China, for the information that the great bulk of the Chinese eat about 3 oz. or 4 oz. of fish a day, while the rest of their diet consists of rice. He says they are fine, big, and strong men, and more than a match for an average or even a picked British sailor, the only Briton generally available for comparison; and he adds that their wounds heal easily, and generally by first intention. A similar record with regard to the Turks as to their great powers of endurance and wonderful vitality in resisting wounds, is to be found in the 1897 numbers of the daily papers. Thus in the *Standard* of May 6, 1897, we find: "The doctors also remark upon the extreme rapidity with which their patients recover from their wounds, and attribute it to the abstemious lives they lead, drinking no wine and eating very little meat, but plenty of vegetables."

Here again in England, do we not die younger, and in greater

number than there is any necessity for? Are we not afflicted with an infinite number of diseases which cause far more pain and misery than is at all necessary? Are we not given to all kinds of debauchery and excess, and have we not huge asylums full of lunatics and prisons full of criminals?

I look upon all these things as serious and widespread diseases in the human race, and, as I am not one of those who believe that Nature herself, if she had a free hand, would tend to destroy us, but rather to preserve what is good, and eliminate what is evil, and, further, cannot believe that the tendency to these evils is part of the ground-plan of Nature's work, or that the unalterable bias to have headache, epilepsy, mental depression, mania, and their results—murder or suicide—alcoholism, morphinism, cocainism, &c., is originally implanted in our nerve centres, I am driven to the conclusion that not a few of these evils are the result of unnatural conditions, and that prominent among these is unnatural diet, the evil action of which we are now in a position to follow out more completely through a knowledge of the powerful effects of urates on the function and nutrition of the whole body.

Such a provisional conclusion is justified by my own experience and results. I was originally told that my tendency to headache, high arterial tension, and other evils was inherited—in fact, a part of my structure and function, which, though it might be modified and relieved by drugs, could not be eradicated; and no one ever suggested a radical change of diet.

By great good fortune, and more or less by chance, I found out that a change of diet was the one thing needful, and what is practically a complete cure has resulted. I have now only one subject for regret, namely, that I did not find this out earlier in life, as I cannot undo the evils and injuries that were accomplished while the warnings of functional disturbance remained unheeded, through ignorance of their causation.

No doubt during this period many defects and deficiencies inherited from several generations of ancestors equally ignorant on matters of diet were increased and intensified, and actually became parts of my organic structure because I was allowed to grow and develop on poisons instead of foods. The factor concerned with my headache that I inherited was probably a slight variation in the size and distribution of the arteries at the base of the brain, rendering my intracranial circulation liable to be affected by unduly high blood pressure;* the other factors in its causation were improper food,

* *Brain*, Spring and Summer Number, 1893, p. 250.

impure blood, and consequent increased blood pressure; but the improper food being done away with, the "neurosis" became a matter of history, in spite of the anatomical factor, which remains as before. I notice also a very interesting clinical note by Dr. David Drummond, of Newcastle, in the *Lancet*, 1897, vol. i., p. 1338, on "neurotic" symptoms of uricacidæmia in the young, in which he exactly describes the headache, epilepsy, cold hands and feet, low surface temperature, high blood pressure, and slow pulse mentioned in previous chapters, and finds them associated with meat eating and excess of uric acid in the urine, and cured by milk diet, and, as he tells us he had formerly treated the neurotic element in such cases with unsatisfactory results, his observations confirm my own in every respect. He also notices a symptom which I have not, namely, diminished knee-jerk, apparently in association with mental and bodily depression and lethargy.

I believe that much the same argument applies to nearly every disease mentioned in this book, and that while certain anatomical or physiological peculiarities may undoubtedly dispose certain individuals to suffer sooner than others, or in one way rather than in another, nevertheless the food factor is common to all of them, and its adequate consideration and treatment will result in prevention or cure. The first step towards this object is the full and complete recognition of the fact that for all practical purposes they are diet diseases, and that gout and rheumatism, for instance, may depend quite as much on the inheritance of the dollars necessary to obtain meat and wine as of any anatomical or physiological peculiarities.

The distinguishing mark of troubles due to collæmia is that they are temporary and periodic, with intervals of complete freedom. When they are chronic and continuous there is an organic factor,* the collæmia merely causing surface fluctuations in its effects.

Everything now depends on the nature and extent of the organic factor and whether removal of collæmia and uric acid irritation will allow of its improvement, or whether such improvement is in the nature of things impossible (*e.g.*, serious pericardial or valvular lesions of the heart, or ulceration, adhesion or other chronic irritation in abdominal organs, cerebral tumour, thickening of membranes, &c.).

We have seen that serious heart lesion or weakness renders the prognosis hopeless in Bright's disease or diabetes, and the same

* See "The Organic Factor in High Blood Pressure," *Medical Record*, New York, February, 1908.

holds for other collæmic troubles which are thus complicated. Thus a mental depression, which is temporary and periodic with a strong heart, becomes chronic and continuous with a weak or diseased one.

Might it not be worth while to make a determined effort to treat our criminals (who are often criminals only because diseased) with a uric-acid-free diet? If the alteration in their cerebral circulation is functional, it will do more than anything else to remove it; and if after that has been done they look at life and the world from a different standpoint, the practical knowledge how to live cheaply on an unstimulating diet may be of no small advantage to them; and lastly, it will, or should, greatly diminish the cost of maintenance. And, if I mistake not, the cost of disease and crime already presses heavily enough on the less diseased portions of the community. Then precisely the same will apply to our vast asylum and poor-house populations; the inhabitants of the former must often owe their disease to unsuitable diet, acting in the manner depicted in previous chapters over one or more generations; and the tenants of the latter may owe their poverty in no small degree to a life-long habit of spending their money on stimulation in place of nourishment, thus constantly losing both in power and pocket.

I see plenty of poor women who live from week's end to week's end on little but bread and butter; but the husbands of these women still think that it is impossible to do a labourer's work without beef and beer, and know but little of the nourishment values of cheese and breadstuffs, a position about as far from the truth as it is possible for an ignorant man to arrive at. About one-half of what the man spends on stimulants would provide both himself and his wife with all that nourishment requires. Then, in spite of his insular position, the British workman is even now suffering reverse after reverse at the hands of the foreigner, who has learned from stern necessity the lesson of cheap living.

I am very pleased also to be able to add that quite a large number of fellow sufferers have now had experience similar to my own—not that the diet is successful in every case. I have never met with any treatment which could honestly lay claim to so large a proportion of cures. Some are unable to alter their diet, being unable to eat at all when a change is attempted; others apparently alter their diet and yet are not cured, but these cases are the exception, and require further investigation before anything definite can be said; and I sometimes find that such cases have been making the mistake of continuing a little meat or fish, or, in the

case of ladies, some tea. On the other hand, a considerable number of sufferers in the profession have applied my suggestions to their own cases, and report that they have every reason to be pleased with the result. One of these concludes a letter by saying: "Beyond doubt I have established the fact that much, if not all, of my ill-health and moral disturbances were caused by eating butcher meat, the metabolic products of which I was unable to eliminate."

I quite appreciate the caution of that "if not all;" at present we can only suggest that what is removed by change of diet is due to wrong diet. Only after several generations of contrasted diet will it be possible to say how many generations back this tendency to headache, epilepsy or depression really originated, and whether it would have originated just the same had our ancestors lived without flesh or stimulants. In the generations we see to-day these things are strongly hereditary; how many generations of correct diet will be required to put a stop to this?

Another professional patient writes, after narrating other cases in which the treatment has been equally successful: "Personally my debt to you and to the theory is a heavy one. Four years ago I was an old man at 37, with the enthusiasm and vigour of life quite crushed in me, retired to a pottering country practice to eke out a miserable existence. All that is now thrown to the winds, and I am back to town work in the forefront of the battle, and with the keenest enjoyment of life."

This record shows us how much those who do not lose their lives may yet lose in the mental and physical enjoyment of them, by remaining the slaves of diet and the victims of collæmia.

Speaking of morals reminds me of the very moderate and much needed warning given by Dr. Keith ("Fads of an Old Physician," chapter xiv.) with reference to the effects of high living on the morals of the young, which my own experience leads me to endorse most thoroughly (see also chapter viii.).*

I have also heard from my friend Dr. W. Young, of Wellington, N.Z., of the case of a man, aged 50, who some three years ago suffered from headaches and loss of energy (collæmia of decline of life), and then adopted a system of treatment by cold baths with abstinence from meat. The result was that he soon got a distaste for meat and left it off altogether, and Dr. Young, who met this

* I was interested to see that in a discussion in the *Lancet*, 1897, vol. ii., p. 685, on schoolboy morals, one of the writers advocated a reduced allowance of meat; but I fear that the tide of custom at schools and colleges still runs strong in the opposite direction.

man while attending his wife, goes on to say: "He is very pleased with the result of the three years' vegeterianism, and says that though during these three years he has lost weight, yet he feels stronger, and is more energetic and rarely has a headache. The improvement he attributed to the baths."

I think the author of the above-mentioned system is to be congratulated on his knowledge of human nature, for this man would not have altered his diet except to help the baths; and would have indignantly repudiated the suggestion that he was eating meat, which did not agree with him. Of course he had been eating it all his life, and knew much better than that! The case is a beautiful illustration of the value of the oblique method in dealing with people who are absolutely ignorant and full of prejudice.

There is an interesting article by Dr. W. A. Potts on the advantage of a purin-free diet, in the *Lancet*, 1906, vol. i., p. 1636, in which he gives details of several cases and concludes that the method of treatment by excluding purin "will be found of real value and deserving more general application than it has yet received." I am glad to see that he also says that it requires care and discrimination in its application, that careful record should be kept of weight, and that clinical tests should be instituted to measure progress.

An enthusiastic patient sends me the following notes of a Swiss climb. He says: "I successfully climbed the Wetterhorn, partly because I love mountains, glaciers and glorious scenery, but partly to demonstrate that a rather delicate and sedentary Londoner, who lives on wholesome foods and avoids poisons, can undergo a great strain with impunity"; and then he adds: "I am the first person who has done the climb in winter for two years. One of my two guides had a narrow escape from frost-bite and the other suffered from pains in the foot on the day after the descent." Further on he says: "I am a little proud of one fact. I did the business on bread and cheese and two bottles of milk, at the total cost of about 1 fr. The guides required, for two days, five bottles of alcohol (four of wine and one of cognac), 10 fr. worth of meat, tea, coffee, &c., costing in all nearly 54 fr. No wonder they ran risks of frost-bite."

I have also an interesting record from another patient, this time a Fellow of a Royal College of Surgeons, of the most marvellous effects of diet in relieving what had been considered incurable morbus cordis, which appears, so far as I can judge from the description, to have been chiefly due to collæmia, but space quite fails me to do anything like justice to this and other interesting records

which I have received from many sides. I shall no doubt presently be obliged to publish a volume of clinical cases as a supplement to this one.

I might also mention that I have records from some of those who live in country districts and work among the poor, of most marvellous recoveries of one or two men of more than 80 years of age who, having been crippled by arthritis, are able, owing to the diet, to throw away their sticks or crutches or to carry them over their shoulders, and of others who could not expect to live more than a few weeks and who are now going strong and healthy.

I see with great interest that Dr. Watson, some of whose conclusions I ventured to criticise in a former chapter, has published in graphic form some most interesting statistics on the increased consumption of animal food in the past fifty years, and he says: "Study of the available data proves conclusively that in the last fifty years there has been an enormous increase in the consumption of animal food (meat)." He gives also the quantities of tea and coffee taken for a similar period, tea having increased from 2½ lb. per head to 7 lb. in that time. He also says: "The writer has been told by more than one practitioner of large experience in India that appendicitis is almost unknown among natives in the districts in which the staple article of food is rice; similarly that chlorosis is extremely rare."

The Japanese and their habits as to food and mode of life have been much discussed of late, for everyone has been struck by their very remarkable feats of strength and power of endurance, and no less by their remarkable display of mental activity, artistic talent, and power of military organisation; and as a result of the interest which has thus been centred upon them it appears to have been shown that their diet contains much less uric acid than that of the average Englishman of the present day, and that they live in many ways far more healthy lives than we do, and that perhaps it is the result of these methods and modes of life that they are to a considerable extent free from rheumatism or the local accumulation of uric acid, and also from mental lethargy and bodily fatigue, the circulation effects of the same poison. Their power of endurance especially seems to be in all probability second to that of no other race in the world, and those who say uric acid is often a question of one man's meat being another man's poison should compare the strength and power of endurance, the freedom from disease, and the mental activity of the Japanese with the absence of many of those good qualities and the general lethargy, debility and invalidism

of their own countrymen. It is safe to say that the fields of Japan are not disfigured by advertisements of endless drugs as remedies for the numerous ills which thicken around an invalid and decaying race. Those who make a rich harvest by poisoning people with extracts of dead carrion, or those who by their vaunted remedies make an equally rich harvest in trying to patch them up again, would have no chance of making a living in Japan.

There is one interesting habit which the Japanese, especially those among them who are going in for athletic training, are said to indulge in, and that is drinking large quantities of water. I mention this merely to point out that it would not be at all a safe habit for people living in this country and on different food to indulge in; for the Japanese, with his free capillary circulation, can really wash himself out with the water he drinks, and it may often pass through him almost as fast as he drinks it. But the average Englishman must not imagine that anything of the same kind would occur in his case; if he were to drink such large quantities of water his capillary circulation, which is slow because blocked with excessive uric acid, would not allow the water to pass, and it would remain in his body, dilating the stomach, the heart, and the blood-vessels, and producing headache, depression, apoplexy, and all the more terrible dangers of collæmia and high blood pressure, and eventually, through more and more water and higher rise of blood pressure, he would suffer from incurable dropsy and hopeless and permanent dilatation of the heart. When the Englishman has learnt to copy the Japanese and swallows only one-fifth or one-sixth of the uric acid he now pours into himself in a day, there will be the very best evidence, in his improved health, strength, mental activity and acuteness, that meat and tea are poisons for all who take them; and that this food has been selected merely because the real action of uric acid has been overlooked owing to its producing differing effects according as it remains in solution in the blood stream or is deposited in the viscera and tissues.

When a gouty man swallows uric acid or meat which contains it, it does, for reasons which I hope are now well understood, not remain in solution in the blood, but is caught up in the liver and other tissues, and the result of this will be that the uric acid filter thus formed will continue to keep the blood clear for a considerable time; hence both collæmic and arthritic troubles will be diminished, and the patient will say, and say truly, that he has been cured of the gout by a meat diet; but the uric acid thus swallowed and all the uric acid previously in the blood has not been destroyed, burnt

up or oxidised, or suffered any other fate proposed for it by the scientific imagination; it has merely been added to the deposits already present in the liver and fibrous tissues, and these at some future time must again be taken into solution in the blood, when more severe collæmia and worse arthritis will result. Some consider that there is a limit to the amount of uric acid which can be retained or held back in the body, and no doubt there is such a limit; but those of us who have had much experience in the hospital *post-mortem* room will have no doubt that many pounds of uric acid can be stored almost all over the body before this limit is reached. And it follows from the first principles given in the earlier chapters of this book that the more uric acid there has been already retained in the body and the more numerous the foci of retention, the greater will be the power of the uric acid filter action and the greater tendency will there be to retain. Thus, the more uric acid the man has in him the more he will retain and the less he will excrete out of his daily turnover. Here we see the enormous importance in gout or rheumatism and all retention diseases of clearing out to the utmost possible extent all the foci of retention that have been formed. But such retention postpones collæmia almost indefinitely, and thus uric acid has been looked upon as a stimulant possibly, but not as a depressant poison.

With regard to alcoholism, I think the vegetarians can make good their claim that the adoption of their diet does as much to cure this trouble as anything that is known, and the reason that it does so is simple enough.

Here, again, how much originates in the individual, how much originated several generations back? I have known monkeys who became habitual drunkards; no doubt they were on unnatural diet, but it is unlikely that they had many ancestors addicted to alcohol.

Meat, as I have said in chapter iii., is a stimulant, and causes a fluctuation in the excretion of uric acid; its stimulation is due to retention of uric acid, because, as we have seen, every drug which clears the blood of uric acid is a stimulant; but this is followed by a corresponding and more than corresponding depression, when the urate driven out of the blood gets back into it along with the urate introduced in the meat itself.

For the relief of this depression more meat must be taken, and when meat begins to fail in causing sufficient stimulation alcohol is added; when alcohol begins to fail morphine or cocaine are called in, and so on down the road to ruin.

Now vegetarianism cuts through this vicious circle by making it

impossible for there ever again to be any great excess of uric acid in the blood, and so removing a cause of the depression which leads to the craving for stimulants.

But even this is not quite the whole story, for meat is not only a stimulant, it also causes thirst. We have seen that every drug that clears the blood of uric acid causes diuresis, that this leads to concentration of the blood, and that thirst is the expression of the blood's wants, and goes along with diuresis (chapter ii.); therefore the meat eater is always thirsty, and if he from one cause or another—occasional depression, it may be—acquires the bad habit of quenching his thirst with alcoholic drinks, he soon gets too much of them.

The vegetarian, on the other hand, is not often thirsty, because he is not subject to urate fluctuations and diuresis, and also because the fruits in his diet list themselves supply him with a large amount of water.

My own practice is not to cut patients off from any form of alcohol they may be taking when they come to me, as I know that after eighteen to twenty-four months of a correct diet they will cease to feel the want of stimulants and will give them up of themselves. My personal experience is identical, for on meat diet it used to be one almost continuous course of tonics and stimulants, from May to October (*i.e.*, in the collæmic season) each year; now I never touch one or the other because I feel no desire for them; they seem to be quite unnecessary, and if taken, merely make me feel uncomfortable.

In reference to the term vegetarian, it is evident that I am not a vegetarian in the strictest sense, because I take some milk and cheese; on the other hand, I differ greatly from many who call themselves vegetarians in this country in not taking eggs, pulses, mushrooms, asparagus, tea, coffee, cocoa, bran tea, and other vegetable substances which are stimulants because rich in xanthin compounds.

I am only concerned in these diets and -isms in so far as they bear on the prevention and treatment of disease, and so far as these are concerned pulses and eggs are as bad as meat. I prefer, therefore, to call mine the "uric-acid-free diet," to emphasise the points in which it differs from vegetarianism.

I am also decidedly of opinion that still better results would be obtained in the prevention and treatment of alcoholism if a uric-acid-free diet is substituted for a vegetarian one containing pulses, eggs and tea. The latter is nothing but a stimulant, and if stimulation is, as I believe, always wrong, it is doubly wrong in cases where it has already led to abuse.

Stimulation, as I have said in "Diet and Food," is not strength, but only force rendered a little more quickly available. A stimulant calls out the reserves, it introduces no fresh force into the body, and when the reserves have been all called out a stimulant will produce no effect at all. On the other hand, a food digested and absorbed introduces fresh force from without.

A stimulant has thus to be constantly increased to produce the same or even a diminishing effect, and the more uric acid there is in the body the more stimulant is required to keep it at bay. On the other hand, half a pint of milk produces the same amount of force time after time as often as it is repeated and digested.

Those who do well on the diet soon lose all desire for stimulants, and give them up of their own accord; but others, especially those who are unable to take the proper quantities either from dyspepsia or loss of appetite, will probably have a craving for stimulants from time to time, so that I have come to look upon a craving for stimulants as a sign that the patients are not doing well on the diet. Those who are properly nourished on the correct amounts of uric-acid-free food never want stimulants. I may mention here that patients who change their diet often seem to fall into two classes: those who at once do quite well and go right away without any mistake or discomfort; and those who are more or less decidedly worse for the first few weeks or months, and get better later on. The first class sometimes do well for long periods, as a year or eighteen months, and then they fall off and have periods of depression and trouble. The explanation of these two classes is, I think, quite simple. The first class are stimulated by diet or take to it at a favourable time of the year; they like the new foods, and are at once well nourished upon them, and perhaps take too much fruit. Hence they do not clear out their stores of uric acid at once and they have no initial depression and debility, but later on they flag on the diet if their appetite fails or they get tired of any of the foods; they may then run down, their nutrition may flag a little, and their old stores of uric acid may then begin to pass into their blood; and those who do not understand the meaning of this may be greatly disappointed, because they have already been a year on the diet, and yet for a time are almost as bad as they ever were. It is, I fear, in all cases necessary to get clear of the old stores of uric acid. Those who begin to clear it out at once will feel less well at first, but they improve later on, and then remain perfectly well. The others are well at first, but clear out later on, and are then for a time less well.

There is still another class, and this is, I think, the best of all,

viz., those who have only small accumulations of uric acid, or who clear their accumulations out so slowly and gradually through months or years that the clearing out never produces any serious discomfort at all.*

In illustration of some of these points I give a few extracts from a report furnished me by a gentleman, aged 42, living in the West Riding of Yorkshire: "As the result of five years on the uric-acid-free diet I noted the cessation of all the ailments previously mentioned (a long list), except that I have a slight cold and a little pharyngitis at least once a year. My headaches gradually diminished in severity the first twelve months, and I have never been incapacitated by headache since, except on two occasions: one the day following an excessive amount of gooseberries, and the other as the result of remaining too long in the hot room at the Turkish baths. My working powers have been immensely augmented, while my occupation is a full source of pleasure. The greatest effect of the change is that on strength and endurance. The first four years of my cycling career as a tourist, I often reached home after fifty or seventy miles fagged out, occasionally returning by train on the hottest days suffering from terrible headache. During the past four years not only have I never been incapacitated by headache when cycling, but have been without the feeling of fatigue, so that I frequently ride eighty miles a day and arrive at my destination quite fresh.

"On July 1, 1904, in my forty-first year, without any training whatever, I left home at 1 p.m. and rode to London, a distance of 200 miles, only stopping for meals, reaching the city within twenty-two hours of the start, my bicycle and luggage weighing 50 lb. I do not imagine that this is a feat, but just to show what a middle-aged weakling can do in physical endurance. I reached London quite well, had a good dinner, attended two business meetings, and retired at 10.30 p.m. and slept soundly till 9 a.m. I sleep soundly, but not so long as I used to. I wake feeling very fresh. Although in my forty-second year I feel younger than I did twenty years ago."

I will now say a few words as to the most useful drugs for clearing the blood of uric acid. Of the drugs which have this effect, I prefer the iodides and chlorides, mercury in some form, or the iodide of mercury, or, if it is necessary to act quickly, the nitrites or a subcutaneous injection of morphine.

If there is any good reason for not using mercury, other metals,

* To aid the attainment of this result I give, as appendices, the notes and scheme for alteration of diet I commonly use.

as copper, zinc, silver or gold, or their salts, may be used with good results as regards uric acid ; and I have no doubt that the tonic action of these and other metals is due to their effects on the solubility of uric acid.

The iodides seem to be specially useful where the effect has to be kept up over a long period, as in relieving the high blood pressure of chronic Bright's disease. Ammonium compounds, especially the chloride and certain phosphates and sulphates of the alkalies, lime, &c., are similarly useful, and it is often possible to keep them in action over longer periods than the salts of the metals. In this connection it is interesting to note that a substance called anti-sclerosin,* composed chiefly of retentive salts like those just mentioned, has been produced in Munich and used together with milk diet or diminished flesh in the treatment of arterio-sclerosis, which, it is suggested, is due to deficiency of salts in the blood. No doubt it lowers blood pressure by diminishing collæmia, and must often produce arthritis in doing so. When it has cleared the blood the pressure is lowered, and vascular strain and damage are thus diminished. Arterio-sclerosis is the ultimate result, which is put off if the cause is removed for a time.

Thialion, a compound prepared by the Vass Chemical Co., Banbury, Conn., U.S.A., probably acts in the same way as anti-sclerosin, and has been found useful in many conditions associated with collæmic high blood pressure and scanty urine. It is said to be composed of sodii sulph. and lithii cit., both, as we know, powerful retentives. I think that an alkaline retentive, or more correctly, one that increases the alkalinity of the blood and diminishes the acidity of the urine (see fig. 14), may be tolerated by an irritated (gouty) stomach, when an acidity-increasing combination, like anti-sclerosin, is not. Anti-sclerosin increases the phosphates in the blood; thialion diminishes them; both clear it of uric acid. Sodii sulph. is common to both substances, and is probably the most active ingredient in anti-sclerosin ; but the lithii cit. is evidently a most important addition to it, for thalion adds a precipitant to the blood (sulphate) and removes a solvent from it (phosphate), and is thus a powerful retentive compound. Mercury is useful in the same way in headache or mental depression and iodides in asthma.

All these drugs, however, have the drawback that their action is followed by a rebound when they are withdrawn ; the uric acid which they clear out of the blood is not cleared out of the body, and if the drug is withdrawn the blood soon takes up the uric acid which has been accumulating during its action in liver, spleen and joints.

* Obtainable in London from Reitmeyer & Co., 63, Crutched Friars, E.C.

The best way out of this difficulty is to alternate these drugs with a course of salicylate of soda, which eliminates the uric acid and prevents the accumulation from becoming very large. But retentive drugs continued with a uric-acid-free diet do well, as we have seen in the case of Bright's disease.

The incoming urate being greatly diminished, the old accumulations are gradually eliminated, as introduction is also an important cause of retention, and elimination may be so gradual that collæmia is never severe.

Salicylates are themselves useful in lowering pulse tension and clearing the blood of uric acid; but their greatest effect in this direction takes a day or two to come out, for, during the first two days of their action, while the excretion of uric acid is large, the urine is scanty and the capillaries are not so free as they would be under drugs of the mercury and iodide class, which clear the blood of uric acid to some extent within an hour or two. Later on, as uric acid excretion lessens, we get freer capillaries and a diuresis.

Salicylates are useful also in headaches to follow the morphine or mercury that has been used at first, and remove the uric acid they have retained, and in the same way they may be useful in mental depression; and they may completely prevent fatigue, and will relieve it and its myalgic pains when present.

In a word, it might be said that iodides, sulphates, chlorides and bromides, with mercury and diet, will cure all the diseases in the first fourteen chapters which are due to excess of uric acid in the blood, and that salicylates or alkalies followed by diet will cure the rest.

In albuminuria and Bright's disease, salicylates, when they increase the excretion of uric acid, make the urine scanty and the albumin appears to be increased; but I have never been able to satisfy myself by actual estimations that there was in these cases much absolute increase of albumin. Still, in these diseases I generally prefer drugs of the iodide class, and only use salicylates occasionally to clear out accumulated urates.

Of the use of salicylates in rheumatism, glycosuria and diabetes I need hardly say any more, and in gout I believe that they have only to be given in proper cases and conditions and in sufficient doses to have their powers fully appreciated. I am glad to see that Professor Tyson, of Pennsylvania, considers them by far the best remedies in this disease (*Therapeutic Gazette*, November 15, 1895), and the cases narrated in chapter xvi., in which they failed, will serve to point out the conditions in which similar failure may be expected and the means of avoiding it.

I will not go minutely into the drug treatment of each condition, for, in so far as any of these diseases are due to uric acid, the only real treatment is that by diet, which is both preventive and curative, while drugs for the most part relieve only for a time, and the trouble will return when they are left off.

Practically those who live on natural foods and also guard against excess by occasional temporary fasts, will not want drugs for dyspepsia, nor soporifics for insomnia, nor tonics nor stimulants for debility, lethargy or anæmia; they will live uniformly busy and happy lives, and have also considerable immunity from infectious and contagious disease, and almost complete immunity from their serious and deadly sequelæ.

If any of the troubles in the first fourteen chapters are associated with a slow capillary reflux and scanty urine, the presumption is in favour of an excess of uric acid in the blood, and this and the urine may be examined; but if this is impossible, the temperature in the mouth and rectum may be taken as a guide (fig. 5), and drugs may be given which would have the effect of clearing the blood of uric acid, and their effects on the temperature observed; or, on the other hand, caffein or uric acid in some other form may if necessary be given to see if it eventually makes matters worse, *e.g.*, a patient given caffein as a heart stimulant (and all retentives are heart stimulants) comes out a little later with a gouty irritation of the skin, thus duplicating the results Sir A. Garrod produced with urates. When the diagnosis has thus been fortified, treatment by drugs and diet may be proceeded with.

Dyspepsia may complicate any or all of these conditions, and when it is severe may to some extent prevent drugs from raising the acidity and clearing the blood of uric acid.

It will not, however, interfere with the drugs which are independent of acidity, such as mercury and other metals, whose uric acid compounds are insoluble, unless it prevents their absorption from the stomach and intestines, and in this case mercury can be administered in other ways.

In all cases, however, it is necessary to reckon with dyspepsia, and if possible to cure it; it is partly a cause and partly an effect of the excess of uric acid in the blood, and it fortunately happens that the diet and many of the drugs which are useful for collæmia will also relieve or cure the dyspepsia; for instance, my so-called bilious attacks, with the congestion of the liver and the dyspepsia which preceded and accompanied them, have disappeared along with my headaches.

Dyspepsia also must be kept in mind, both in gout and rheumatism, and in chronic rheumatism it is often an important factor; it keeps up more or less constant excess of uric acid in the blood (hence its important effects in the production of anæmia), and when, owing to formation of acids, exposure to cold, or other cause, a rise of acidity retains some of it in the joints, this deposit acts as a uric acid filter, constantly taking more from the blood and increasing the joint irritation. Dyspepsia may also be treated by altering the meals in the way described with reference to fig. 74.

The treatment of uræmia is, I think, the treatment of high blood pressure, together with more or less œdema of the membranes and excess of cerebrospinal fluid, which have been caused by the high blood pressure; the treatment of the high blood pressure may be the same here as in other conditions; but it may be necessary to do something more to remove the œdema, and it seems probable that venesection would be the most likely thing to succeed, for it would not only complete the reduction of blood pressure, but would probably cause the blood to take up available fluid from all directions; and we know that morphine and venesection have been found useful in this and kindred conditions. Uræmia also has occasionally been observed to terminate in an attack of gout, which of course would mean the practical clearing of uric acid out of the blood and relief of high blood pressure (see paper by the late Dr. Ralfe in *Transactions of the Medical Society of London*, vol. xvi., p. 216; and *Lancet*, 1893, vol. i., p. 415; also case in *Lancet*, 1889, vol. ii., p. 1118).

I have mentioned in several places (chapters ii., iii., and iv.) some points in the pathology of gravel and stone, and I shall now merely remark that whatever the influence of other factors, an excessive excretion of uric acid is not very rarely the most important point in their causation.

Thus they are met with in old people who have suffered for years from gout and other signs of excess of uric acid in their body and blood, and are a natural result of failing metabolism in such people. Thus those who have much urate in their joints may, as appetite and digestion fail and their acidity runs down, excrete for weeks and months an excess of uric acid till the joints, which at one time were full of urates, show nothing but empty erosions of cartilage (see chapters v. and xv.).

As the excess of uric acid from this source passes through the blood, it obstructs the capillaries and diminishes the flow of water from the kidneys, so that we get a large excretion of urates and

very little water to carry it off, and it is little wonder that some of this urate is occasionally deposited in the kidney or the passages below it; and as I have shown in reference to fig. 64, it is the uric acid which controls the excretion of water, and not the water the excretion of uric acid.

Now this is a very painful and troublesome condition, and one with which it is very difficult to deal satisfactorily; thus it may be difficult to stop the plus excretion of urates, for the patient is often so feeble and his acidity so low that acids are overpowered; but mercury and iodides will act, and these will not only diminish the excretion of urates, but will, at the same time, increase the excretion of water. Soda and potash may be given, but they will not increase the water, and will increase probably the actual excretion of uric acid.

The urates are probably doing no harm in the joints, and nothing will be lost by letting them stay there a little longer, or by allowing them to come out into the blood and urine more gradually, so that I am inclined to think that the iodides or other retentives, together with diet, form the best line of treatment to adopt. I am here speaking merely of the greater or less excretion of urates from gouty joints and other places of deposit in the body, and not of the treatment of a calculus in the kidney or bladder already formed; the line of treatment I suggest is intended to prevent their formation.

As regards mere expulsion of the calculi when formed, Dr. Hermann, of Carlsbad, has pointed out that large doses of glycerine (1 to 4 oz. by weight) are often very useful (see *Medical Chronicle*, January, 1900).

It is an obvious conclusion from my reasoning, that if a patient such as we find thus suffering from gravel in old age had altered his diet twenty or thirty, or better fifty or sixty, years before, he would in all probability never have suffered either from gout or from gravel.

I am indebted to my friend, Captain Ernest Roberts, I.M.S., for the following interesting observations with regard to the effect of diet on the incidence of calculus in India.

Among the poorly nourished, rice-eating population it is rare. Among the wheat-eating, meat-eating and generally better fed provinces it is frequent; and in these provinces it is specially common among the men and boys, rare among the women and girls; and this is largely due to diet, for the men feed best and the boys with them, the women have their leavings, and the girls what they can get, the last-named being very little thought of and badly fed.

It seems to me that this is extremely interesting, for in the meat-eating provinces there is most introduction of uric acid, and those introduce most who are best fed (men and boys), and those introduce least who are least fed (women and girls); and then the warm climate of India conduces to high alkalinity of the blood and the relatively rapid passage through it of all the uric acid introduced; and it will be excreted most quickly and completely in those least well fed, and retained and accumulated most certainly in those who are best fed.

During the discussion of a paper which I read at the Medical Society in November, 1896, and in which I suggested that "the uric acid diathesis" was a myth, inasmuch as all the diseases referred to it are really due either to the excessive introduction of ready formed uric acid or the excessive consumption of albuminous food, both of which dietetic errors can be corrected, and the diseases due to them removed, I was asked by Mr. Freyer, who appeared as a champion of the "diathesis," how it was that many of the natives of India, who lived on exactly the kind of food I advised, yet suffered severely from stone. After what I have said with regard to the effects of excess of albuminous food (*i.e.*, of excess of quantity without reference to quality), and especially after my remarks on figs. 74 and 75, I do not think that the question requires any further answer; but the discussion thus begun was continued afterwards in the *British Medical Journal*, and was brought to a close with the publication of the most interesting letter of my friend, Captain E. Roberts (*British Medical Journal*, 1897, vol. i., p. 625), and in this discussion several facts of considerable interest were brought to the surface.

First of all it became evident that in spite of adverse criticisms the above-mentioned habits of the natives in feeding the men and boys best really exist, and no doubt account both for some extra introduction of uric acid as well as possibly for some excess in albuminates in males as compared with females; that more meat is really eaten by the natives of India than might be supposed; that large numbers of Mohammedans eat it regularly and that the lower caste of Hindus take it whenever they can get it: and I am also indebted for corroborative evidence on these points to my friend, Dr. Bonus, and his brother, General Bonus, who served in India for many years in various official positions and thus came into contact with the natives in various parts of the Empire.

And, speaking generally, it seems to be just in those meat-eating portions of the population that stone is most common. Further,

Captain Roberts shows in the letter above mentioned that stone is most common in the districts where wheat is the staple food, and least common where rice is the most important food, and I may mention that Parkes gives the percentage of albuminates in rice as 5, while in wheat flour he gives it as 11, or more than double, and it is thus evident that the wheat-eating population are much more likely to get excess of albuminates than the rice-eating (see also remarks in chapter viii., p. 369, on "Causation of Fatigue and Rheumatism in Horses").

Further, it is evident from statistics kindly sent me by Captain Roberts, and which are extracted from a paper on "Vesical Calculus in India," which he presented to the First Indian Medical Congress in December, 1894, that the diet of the native soldier in India, though containing no meat, does, nevertheless, contain nearly one-quarter more albuminates than the diet of the European soldier, and also that in some parts where certain kinds of pulses are plentiful and are freely eaten, the diet of the natives contains a still larger excess of albumens, and will, as we can now see, cause the introduction of quite a large amount of uric acid (see fig. 75).

With regard to some of these points Captain Roberts says, in the letter to the *British Medical Journal* above referred to: "Out of a total of over 4,000 cases of calculus operated on annually in India, one-half are reported from the Punjab, in a population of 20 millions, 1 million of whom are reported by Hunter as rice eaters, 97 per cent. of the arable area being under wheat, barley and millets. Next come the North-West Provinces, with less wheat, but still only 3 per cent. of the cultivable area under rice, which is said (Hunter) to be eaten by 4 millions out of the 47 million inhabitants—a doubtful point to anyone who knows the North-West Provinces—and from this area from 900 to 1,000 stone cases are reported annually; thus three-fourths of the cases are reported from a wheat-, barley- and millet-eating population of about 70 millions (or fewer).

"On the other hand, the ratio of calculus incidence to population is lowest—and there is a huge contrast between the lowest and highest—in Bengal, Madras and Burmah, where rice is the most important food staple. The contrast is seen even in one provincial area, namely, Lower Bengal, for Behar, the western part thereof, which is pre-eminently a wheat-producing and wheat-eating country, furnishes altogether a disproportionate number of the cases in the Bengal statistics.

"In this connection I must add that I have definite statistics

from the Punjab dispensaries, showing that out of a total of 1,446 cases 1,199 were Mohammedans, and only 247 Hindus, a ratio of 5 to 1. These cases were not picked out to demonstrate a foregone conclusion, but are taken as reported. It is difficult to explain this special proclivity of Mohammedans unless the food factor be taken into consideration."

I am told also by others that among the Hindus who abstain from fish, meat, and eggs, and eat largely of rice and vegetables, rheumatism is, like calculus, rare or unknown.

I am inclined to think that in all these diseases of the natives of India the introduction of uric acid in pulses probably plays a far larger part in causation than retention by acids in grain foods, for exercise and climate both strongly antagonise the latter, while they have no effect on the former.

One further fact of interest came out in the above correspondence and discussion, namely, that the ratio of women to men in stone is very close to the ratio of women to men in gout, for if there is any truth in the pathology I have been endeavouring to defend, this must of necessity be the case, for when the urates are in the body they may have arthritis, and when the same urates are being dissolved and passing out of the body they may have gravel or calculus. They are but two stages of one process, and the ratio of women to men affected will almost of necessity be much the same for each.

In India, owing to the effects of warmth on the alkalinity of the blood, plus excretion of urates is the rule, retention the exception, a fact also mentioned by Captain Roberts in his paper on "Calculus"; and there men and boys suffer most from stone because they eat most meat and most albumen.

In England, with its cold climate, high acidity of urine, and low alkalinity of blood, retention of urates is the rule and plus excretion the exception—an exception associated mostly with the debility of advancing life; and here men suffer most from gout because they eat more in quantity, also, in my experience, more—often much more—meat than women, so that they have both excess of albumin and excessive introduction of urates.

And Sir A. Garrod remarks ("Gout and Rheumatic Gout," 3rd edition, p. 212) that when, in the degenerate days of the Roman Empire, women lived like men, they became "the subjects of acquired gout equally with men."

There seems to me in all this just nothing to necessitate the continued existence of the "uric acid diathesis," though doubtless

many will still regard it with some affection, because for quite a large number of years it has played the part of a very respectable and convenient cloak for considerable ignorance.

The publication of the above correspondence also brought me a most interesting contribution of experiences from Surgeon-Major T. Holmested, formerly civil surgeon at Hyderabad, Sind, which he has kindly given me leave to mention. Thus he says: "In Sind all Hindus but Brahmins eat goat and fish and lentils. Stone is very prevalent even in girls. I used to attribute it to chill, for I have had suckling infants with stone" (the youngest he ever operated on being 14 months old).

"In Sind and North India in the cold weather the night and early morning are piercingly cold and midday hot; little children go about naked. The chill, I thought, upset the action of the liver. Enlarged spleen very common in Sind, and fever and pneumonia in cold season."

He also says that fruit and vegetables are deficient in the diet, at least for a large part of the year, in a great part of Central Sind, and that amongst natives a modified scurvy, as shown by the teeth, is common.

I think that Surgeon-Major Holmested is quite right about the effect of chill, which may affect the active metabolism of a child very powerfully; in them cold will act as a stimulant and raise the acidity of the urine; it will probably diminish for several hours the natural morning excretion of urates, causing retention either from day to day or throughout the whole cold season.

The uric acid thus held back will come out either at some other hour of the day or at the end of the cold season with a rush, just as appears to occur in this country in March, April and May, and on to July; and the result may often be insufficient solution and deposition of gravel or calculus.

It is hardly possible to say too much about the folly of exposure to cold. Those who will insist on this practice (the bracing climate refuge of the flesh eaters) will of necessity retain uric acid and eventually come to suffer from colds, influenza, bronchitis, headache, fits, depression, lethargy, and anæmia, the whole gamut of uric acid disease, and this in spite of the most uric-acid-free diet in the world (see also chapter ix.).

The meat eater is, of course, only doing what is best for himself when he goes to a hill station or a bracing climate, or makes his annual visit to Scandinavia, Scotland, or Switzerland. This is for him the only way out of collæmia, debility and anæmia.

But the uric-acid-free feeder is strong because he is sufficiently nourished, and he is free from lethargy, depression and anæmia, and has endless endurance, because he is uric-acid-free; while for him to ape the silly bracing climate habit of the meat eater, which is on a par with the constant tonics, hæmatinics, and stimulants of the xanthin-poisoned, is just to set up a store of uric acid, to undo the effect of the uric-acid-free diet and lose all the good it is capable of producing.

Some years ago an old doctor whom I knew well, and who had been on the uric-acid-free diet for a number of years, got bronchitis in the early spring and died. At once there was a shout from the ignorant and unsympathetic: "Look at this diet, it neither cures nor prevents; Dr. So-and-so has died of bronchitis!"

Unfortunately "Dr. So-and-so" had contracted the habit in his flesh-eating days of bracing himself by means of cold, and foolishly believed, in spite of all I could say, that his strength and endurance (which were considerable) were due to this. I know as a fact that it was his daily habit to potter round his garden in the early mornings of March and April with nothing on but his pyjamas, and I have known others who visited their gardens in the cold mornings with still less clothing on, and equally bad effects.

By all means get as much fresh air as you can; but it is never necessary to expose yourself to cold in order to do this, and, if you insist on doing so, you will soon lose your uric-acid-freedom, which is the real source, not only of strength and endurance, but also of immunity from disease.

The fact that I use a bracing climate just as I do tonics and stimulants to help those crippled by flesh and tea to get into a condition to profit by a better diet, is not to be regarded as an excuse for a stimulant habit. Those who get uric-acid-free must avoid all tonics, stimulants and cold, for to do otherwise is to sacrifice freedom.

There is no need for them to coddle, though heat will make them strong and active, rather than weak like the collæmic, for heat saves a certain amount of food expenditure in keeping up body temperature, and more force is available for other things; but let them put on enough clothing for their exercise to warm them comfortably, for cold is the great evil of a sedentary life, which, as we have seen, leads to gout and collæmia.

The effects of fevers, pneumonia and enlarged spleen in causing increased retention of urates in the body I have already mentioned several times; and a deficiency of fresh vegetables and the alkali they supply will obviously help the other causes making for retention

or accumulation, which in this country, just as in India, furnishes the material for subsequent gravel or stone.

A friend whose experience of diet has rendered him enthusiastic, and who was recently travelling in India, sends me the following, which he said was gathered from talking with many doctors out there: "The Bunnias living on grain (including some pulses) almost entirely are prone to diseases (diabetes, &c.), get very fat and are bad lives. Brahmins, who live on rice, grain, greenstuff and much milk, are very healthy."

"In Rajputana, where it is very dry and very hot part of the year and cold the rest, I saw many signs of gout among the meat-eating native servants." This is, I think, very interesting, and it reminds me that everyone who treats gout to-day cuts off beer and wine (uric acid precipitants) and diminishes meat (a uric acid introducer), while every drug used in treatment, or that ever has been used, for that matter, is a solvent of uric acid, and increases its elimination in the urine. And yet on the same page with this advice one may find the statement that gout has nothing to do with uric acid.

Others, again, say that both gout and collæmia are due to defective metabolism of uric acid in the liver of those who suffer. But this defective functioning of the liver must be almost universal in the peoples of the world, for we see gout to-day in all nations and climates; only where the people are poor and flesh is expensive is it known as "the rich man's disease," but where the people are richer or meat is cheap it is almost universal; and butchers have long been noted sufferers from gout and bad health.

Similarly, in the British Isles, with the cheapening and wider diffusion of flesh and tea, in the last thirty or forty years gout and collæmia have spread in all directions. Formerly, as is still the case in some other countries, they were chiefly confined to the rich, and the term "poor man's gout" is an invention of recent history. Before it was rich man's gout, and the land of cakes and whisky did not suffer. In old times the man who became poor lost his gout along with his money, but with cheap flesh and tea this is no longer the case; yet the rich man who for health's sake lives as the poor did forty years ago (on bread, meal, milk, cheese, vegetables) soon ceases to suffer.

If the poor of any country are free from gout to-day it is not because their livers function better than those of the rich, but simply because they cannot get the foods that produce the disease, for the poor of other countries who can get these foods suffer equally with the rich.

This liver defect must be widely spread, and it cannot be important, for the poor are, and have always been, the backbone and fighting strength of every country, and this is most markedly so to-day exactly in those countries where flesh is most difficult to obtain.

And in other parts of the world it is the same, as Dr. T. Sinclair Browne, of Barbadoes, writing under date March 30, 1900, says: "I tell people that out of our population of 200,000, about 14,000 don't take meat, and a finer body of labourers do not exist. A negro will work all day in the sun and never tire, and they are splendidly developed, with not a bit of fat about them. People here (*i.e.*, whites and Europeans) eat meat three times a day, and if they have no appetite they take cocktails before meals to give them an appetite. They also take no exercise. The result is that rheumatism, gout, dyspepsia, liver, heart and kidney disease abounds in the better classes."

In Cairo, as I saw for myself (January, 1902), it is the same as amongst the natives of Barbadoes: no meat is eaten and rheumatism and gout are unknown; and though this might be to some extent due to the dry warm climate, there is also no anæmia except that due to parasites (ankylostomum), and blood decimals of 6 to 7 and 8 are the rule, as against 4 and 5 here. Is this also due to climate? If so, to what is the severe anæmia from which Europeans suffer in India due? Obviously to the meat, which accounts for all the diseases enumerated by Dr. T. Sinclair Browne in meat eaters of Barbadoes. Our anæmia is not due to our climate, but to our flesh food, and when we carry this with us we are anæmic all the world over. The splendid colour and physique of the Arabs and Egyptians are not due to their climate, but to the absence of meat, and the absence of meat in this climate will produce the same results.

In this country we get some retention, that is, men and boys may sometimes go on introducing excess of uric acid in their food and yet not passing excess in their urine; but then some accident occurs and lays them up, they get a fever, a disease like splenic leucocythæmia, or, later in life, carcinoma, and down goes nutrition and up goes the alkalinity of the blood, and all their urate accumulations pass through it in such quantity as to cause more or less deposit in the urinary passages, as occurred in the case mentioned by Sir T. Lauder Brunton (chapter ii.), or the similar cases in chapters iii. and vi. Some are very fond of the idea of washing out uric acid from the body and passages by drinking large quantities of water,

but I cannot see any evidence that this is of much value, for we see from fig. 3 that considerable quantities of fluid taken in the morning hours do not pass through the kidneys, but remain in the blood till uric acid comes below urea in the afternoon; and yet it is exactly in the morning hours that most uric acid is excreted and most water is required to wash it out of the urinary passages.

I think, therefore, that it is very little use to give large quantities of water, for it gets through the kidney just when it is not wanted, and it cannot get through the kidney when it is wanted, *i.e.*, when large quantities of urates are passing into the urine. Again, the drinking of much water may increase the excretion of uric acid by causing dyspepsia, hydræmia, or both, and thus do harm in gravel and calculus, where our aim should rather be to diminish for a time the excretion of uric acid, and at the same time free the excretion of water, as with an iodide.

Now, when an excess of water (*i.e.*, in excess of normal thirst and the requirements of the blood and tissues) is taken it often causes very marked dyspepsia, possibly by diluting the digestive secretions, and dyspepsia, as we know, causes collæmia and a plus excretion of uric acid in the urine; but in gravel and calculus this is a harmful and not a helpful effect. And, apart from gravel, in other conditions of uric acid disease, I see no reason to think that water drinking in excess is of any real value in treatment, for, as we have seen in previous chapters, it is the uric acid that controls the excretion of water and not the water that controls the excretion of uric acid.

Apart from the dyspepsia it may produce or increase, I doubt whether an extra pint of water swallowed has any effect on the excretion of uric acid in the hours which follow its ingestion; but where people habitually over-eat it may be useful in default of other measures to cause a little dyspepsia and perhaps some increased action of the bowels, so as to sweep out some of their unnecessary supplies before they are digested and absorbed. As an amusing patient said to me some years ago: "What a world it is—one-half dying of too much to eat and the other of too little"; and in all uric acid diseases it is far easier to prevent introduction than, having got it in, to provide for its safe and satisfactory removal. The excretion of uric acid is controlled by its solubility in the blood, and, so far as I know, apart from dyspepsia, excessive water drinking affects this but little, and though, as previously pointed out with reference to the late Sir W. Roberts's

results in chapter xv., the more water there is in the blood the greater power it will have of dissolving biurate deposits; still if such urates are in this way brought into the blood in any quantity and assume the colloid form, they will obstruct the capillaries of the kidneys and allow only a scanty excretion of water to pass with the urates into the urine.

I have thus come to look upon water drinking for the cure of uric acid diseases as practically useless; but in all high blood pressure cases it is not only useless but positively harmful, for obviously the more fluid there is in the body the higher will be the blood pressure, other things equal.

But headache, epilepsy, mental depression, vertigo, uræmia, dropsy, eclampsia, are all made worse by rise of blood pressure, *i.e.*, by increase of fluid; hence the importance of withholding fluid as much as possible in such conditions and of giving a diet as dry as possible of breadstuffs and fruit, and no fluid unless there is decided thirst. To give fluid in such cases with the idea of eliminating the poison is not only useless, but absolutely unphysiological to the extent of being silly.

The effects of exercise on nutrition, metabolism, and the excretion of urea and uric acid I have already gone into at great length in chapter viii., and from the fact that it stimulates and increases metabolism, and improves the circulation through almost all the organs and tissues, it is easy to understand that regular exercise, short of fatigue, should be extremely useful in many of the disease processes of which I have been speaking. Thus in high blood pressure and headache it frees the capillaries and relieves the intracranial pressure; in mental depression Professor Lange has specially pointed out its value; then want of regular exercise is one of the most common causes of dyspepsia, with all its train of bodily and mental ills. Again, in albuminuria and glycosuria so much regular exercise as will keep up the nutrition of the skin, the muscles, and the important glands is often one of the chief points in treatment. In gout also, as we have seen, regular exercise will prevent attacks.

In many cases, then, I consider such regular exercise as second only in importance to diet, and the two can often be employed together with advantage. Where the surroundings or the condition of the patient prevent satisfactory exercise, massage, which is, in many respects, equivalent to exercise, may take its place, and, especially where nutrition is low, it is often an important help at the commencement of treatment. Then, again, massage is extremely useful, as has been so ably demonstrated by the late Dr. A. Symons

Eccles,* in improving the circulation and nutrition in joints and other structures which have been damaged by urates, or have had their nutrition seriously affected by the circulatory changes which these substances produce, thus completing the cure of which the removal of the urates is only the first step, for obviously the removal of urates, while perhaps preventing further structural or nutritional change, will not restore the tissues to their original healthy condition. It is important, however, to bear in mind, as suggested in previous chapters, that massage, by flooding the injured fibrous tissues with fresh blood and fresh and more alkaline serum, may really help considerably with the removal of urate from the tissues and the suspension of the chronic irritation, fibrosis and stiffening which their presence produces and perpetuates; and this may apply equally, whether the original injury of fibrous tissues was uratic or traumatic, or, as so often happens, a mixture of both. And this constant presence of irritating urates may really account for much of the observed difference in the rate of repair of wounds and injuries between those who eat meat and those who live on an almost entirely uric-acid-free diet, the other most important factor being an improved circulation in the absence of collæmia. On the other hand, it is also true that exercise will do little or nothing for the relief of uric acid diseases so long as diet is left unaltered and uric acid is being continually introduced into the blood in excess.

Looking to all these facts it is most difficult to avoid the conclusion that many sufferers from the diseases treated of in this volume owe their sorrow, suffering, and early death to nothing in this world but their own folly. Hence I often say that whatever one may think of a meat eater's humanity and morality it is impossible to question his *bona fides*, for he is so obviously ready to die for the cause. Certainly the meat eater has no right to blame Nature either as to the origin of the troubles or their inheritance; in human nature, just as elsewhere in the cosmos, the punishment follows the broken law, and comparative anatomy should long ago have warned him of his error in diet (see "Diet and Food," ed. vi., figs. 6 and 7).

That it is easily possible to sustain life on the products of the vegetable kingdom needs no demonstration for physiologists, even if a majority of the human race were not constantly engaged in

* *British Medical Journal*, 1888, vol. ii.; *Ibid.*, 1891, vol. i., p. 1075; "Sciatica," Macmillan and Co., 1893; *Lancet*, 1893, vol. ii., p. 924; and "The Practice of Massage," Macmillan, 1895.

demonstrating it; and my researches show not only that it is possible, but that it is infinitely preferable in every way, and produces superior powers both of mind and body as the result of improved circulation in muscles and nerve centres.

But with regard to many of the vegetable feeding races mentioned, we can now see that they would have had a much better record than they have if they had known more about the poisons in vegetable foods; and I have no doubt that the future will demonstrate this fact to their great advantage.

They would also, no doubt, have done better if they had not suffered more or less constantly from insufficient food (see facts previously mentioned).

Hence it is easy for well-fed Europeans to sneer at the small natives of some parts of India; but prevent famine and conditions bordering upon it, and the record might be very different. And as I have shown in chapter viii. the small natives of India not very rarely beat Europeans both in strength and endurance.

I recently came upon this interesting statement in J. J. Rousseau's "Thoughts on Education," C. W. Daniel, London, page 21.

"Among other proofs that the taste of flesh-meat is not natural to man we may reckon the indifference which children have for that kind of nutriment, and the preference they give to vegetable food, to butter, milk, cakes, fruit, &c. It is of the utmost importance not to debauch this primitive taste, and to prevent children from being carnivorous. Were it not expedient upon the account of their health, at least it is a matter which concerns their temper and disposition of mind; for whatever forced construction we may give to experience it is very certain that great eaters of meat are in general more cruel than other people."

Lastly, there is the extraordinary and almost inexplicable fact that most of the advantages of a diet from the vegetable kingdom have been pointed out by one man after another for well on to three thousand years, and their words have apparently fallen on the almost absolutely deaf ears of the meat eaters, from which we may perhaps conclude that the ingestion of these poisons blinds the eyes of its consumers to knowledge and wisdom, and prevents them from realising that they and their fellows are constantly suffering many and terrible things for no reason.

It is true, however, that this knowledge of the ancients was very imperfect, so that in running from one danger they must have often fallen into another. Hence, such success as can now be attained,

is to a corresponding degree an exact measure of knowledge, but there is still plenty to do in improving both knowledge and power.

I should advise those who would like to know what diet may do in the matter of health, strength and power of endurance, both of body and mind, to read Mr. Miles's book, "Muscle, Brain and Diet," previously referred to.

It is practically a record of the effects of my diet by a patient; and this record shows that whereas he was diseased he is now well, and that he has improved quite 50 per cent. in activity and endurance both of mind and body.

His experience is a parallel of my own, but it is much more valuable because, being well known in the athletic world, his powers have always been on record, and he has won championships in America as well as in England.

There can, then, be no doubt about his improvement, and that, as he himself points out, at an age when improvement in games is not generally met with.

Among points of special interest in his record, I note the importance he attaches to the desire for stimulants as a sign of bad health. Thus he says (previous reference, p. 30): "I can positively assert that I consider my health to be not so good as it should be if I can even be induced to take stimulants at all."

Now, this is most certainly true, and there is nothing that I know of that would induce me to take a glass of wine, because its effect would be anything but pleasant, and it would promptly render me dull, morose, irritable and uncomfortable.

And this has, I think, a simple physical explanation, for owing to my diet the alkalinity of my blood is high, and in that blood I have only a little uric acid, and that in good solution with abundant alkali, so that my capillary reflux is quick and my blood pressure low.

But throw a little acid into my circulation (and that is the effect of a glass of wine), and the alkalinity of my blood is reduced, the solubility of that uric acid becomes less complete, it moves in the direction of the collæmic point and tends to blocking of capillaries; hence my capillary reflux slows and my blood pressure rises, with the usual mental results of irritability and depression.

Wine also in those not accustomed to it tends to irritate the stomach and upset digestion, acting like the brandy in fig. 67, and causing irritability and depression in place of stimulation.

We see, then, that uric-acid-free diet not only removes the desire for stimulants, it brings about a condition in which acid stimulants

actually do harm and produce irritability and depression. I not only do not crave for a stimulant, but I hate it because it makes me miserable.

As a result of this experience I now rarely trouble to cut off stimulants in altering diet, as I know that most people who live as I do for twelve to eighteen months will also learn to hate and avoid them.

Then on p. 48 Mr. Miles says: "The better the 'condition' I am in, and the better my games and work are, the more I feel errors of diet."

This also is exactly my own experience, and the cause is, I think, very simple, for we have seen above that uric acid interferes with its own solubility in the blood, and that uric acid is itself a stimulant, for its first effect is to clear the blood of uric acid.

Now, it follows from this that the less the uric acid in the blood the more solvent power will the blood have for fresh uric acid, and the more quickly will any uric acid that is swallowed pass into the blood, combine with alkali and produce collæmia.

Hence those who have got nearly free from any daily introduction of uric acid are much more quickly affected by any chance error in diet causing fresh introduction than those who are constantly introducing a little every day.

And it is only those who, like myself, are nearly free from introduced uric acid, and have plenty of alkali available in the blood, who can test with any accuracy the quantity of uric acid or xanthin in any substance, as I have done in many of the figures in previous pages (see also record by a patient a few pages back).

Mr. Miles, it will be noted, includes pulses in his food list, and after what I have recorded of these in fig. 75 it may be a matter of surprise to some that he attained to such good results while taking them.

But a reading of his book shows, I think, that, like myself, up to the period of which I have given records above, in reference to fig. 75, Mr. Miles did not eat pulses regularly or in any large quantity; and at worst a little pulse once a day is a great improvement on meat, fish, fowl, game, eggs, tea, coffee and alcohol.

Mr. Miles's result was a very great improvement in every direction, but he has not attained, and, indeed, has not attempted to attain, to the greatest possible freedom from uric acid and the best possible results of such freedom.

With much of what he says as to the influence of diet on mental and moral conditions I most strongly agree, and I have quoted the

parallel opinion of others on previous pages, and as I have pointed out in "Diet and Food," life as a whole assumes a totally different aspect for those free from collæmia.

It would now be easy to add a considerable list of athletes who are constantly making records on diets such as those I advocate, but as I have gone into this subject at some length in speaking of training in "Diet and Food" (6th edition), I shall not take up space by repeating it here. It is now possible to say in a moment which athlete of any group is likely to win, for obviously that man will win who has least uric acid in his blood, the most normal capillary circulation, and hence the least friction in his machinery.

Many similar books to that of Mr. Miles have now been written, both in Europe and America, and in Germany books have been written and largely circulated, both by the translator of this volume and others, setting forth the advantages of diet for avoidance of disease and increase of athletic power and fitness, so that the diet is perhaps better known in Germany than anywhere.

A most interesting record of the experiences of herself and others with the uric-acid-free diet has also been given by the writer of the well-known "Pot-pourri from a Surrey Garden," * and she and others have now issued a number of smaller books giving information on the subject of diet, and thus placing it within the reach of all.

So many in this and other countries are now publishing their experiences and advocating the uric-acid-free diet that I think it well to point out that I am in no way responsible for the statements of those writers who have had no scientific training, though I welcome their testimony to the efficacy of the diet in their own and other cases.

I do think, however, that such widespread testimony to the good effects of the diet shows that the subject is quite worthy of more careful investigation by those who have the necessary scientific knowledge. *If* once people begin to think about it, reform will follow. The matter is now so very simple that anyone can see it, and a single glance at the capillary circulation will tell who is a meat-eater and who is not.

The quantity of uric acid in the urine can be made anything we like from 10 to 30 or more grains a day simply by swallowing or refraining from swallowing it, and the capillary reflux and blood granules can be made to move in any direction in proportion to

* Smith, Elder and Co., 1903.

the quantity ingested. When all these points have been realised and by use have become common knowledge, it will be seen how many names and theories of causation have been wasted over alterations of function and structure which are mere results of food poisoning, it not having been possible to see till now that one single poison accounted for them all. It will also be seen that if man had kept to the foods which Nature obviously intended for him this poison would have been avoided; and all so-called disease due to uric acid can be cured or prevented by simply omitting to swallow it, in flesh food, which is unnatural, and in tea, a poisonous stimulant; and the effect of taking these or abstaining from them can now be gauged and tested with that simple implement which was made before knives and forks, the point of the finger.

As will have been gathered from preceding pages, I believe with Shakespeare that meat is as bad for the wits as it has now been proved to be for strength and endurance, with Byron, Trousseau, and others, that it makes man cruel and ferocious, and I think that the condition described by Tolstoy when he says,* "Men of to-day dislike anything reminding them of virtue—and they gladly welcome a doctrine of egotism and cruelty," owes its origin chiefly, if not entirely, to unnatural food.

If this is so, the diseases mentioned in this volume represent but a very small part of the injury that man inflicts on himself when he turns his back on Nature.

* "Essays and Letters." London: Grant Richards, 1903, p. 321.

CHAPTER XVIII.

Instruments and Methods.

It is not my intention to devote space to a general consideration of instruments and methods; I shall merely state shortly those I have used, with a few remarks as to what I think about them.

Acidity of the urine can be estimated with a graduated solution of soda, of which 1 cc. = 6·3 milligrammes of crystallised oxalic acid, and a solution of phenol-phthalein, which gives a pink colour in alkaline solutions.

Process.—10 cc. of urine are placed in a small china saucer, and a drop or two of the phenol-phthalein solution added. The soda solution is then run in from a graduated pipette till a slight pink tinge is permanent. The amount of soda solution used is then read off and multiplied by the number of 10 cc. in twenty-four hours' urine, and this worked out gives the total acidity of the twenty-four hours in grammes or grains of oxalic acid, and this is the way it is recorded in my curves.

Urea.—For this I have used the apparatus of Dupré, which can be obtained from Messrs. Griffin and Sons, Sardinia Street, W.C. Its essential point is that the inner tube which collects the gas has two openings at its upper end, one communicating by a rubber tube with the reaction bottle and another ending in a short rubber tube, which can be clamped just before using, when all the levels have been adjusted.

The chemicals required are a saturated solution of caustic soda and some bromine, which can be obtained in glass tubes containing the exact amount used (2·2 cc.).

Process.—Measure 22·8 cc. of the soda solution and place it in the reaction bottle. Drop in a bromine tube so that it breaks on coming in contact with the bottom of the bottle; remove the broken glass and mix the chemicals by shaking round and round. The result is

a pale yellow solution, which is now ready for use, though if it is at all warm it should first be allowed to cool.

Measure 5 cc. of urine into a small tube about 2 in. long, supplied with the reaction bottle; place it gently with a pair of forceps inside that bottle; adjust the cork in the bottle, and lower the inner collecting tube till the water stands at the line marked 0; lastly, clamp the upper tube of the collecting tube. Now take up the reaction bottle, and incline it to one side so that the urine in the little tube and the hypobromite solution mix, and continue to move the bottle from side to side for a minute or two till they are thoroughly mixed and the resulting effervescence is over. Place the reaction bottle on the table, and allow five minutes or so for it to cool, then raise the inner tube so that the water stands at the same level both outside and in, and read off the amount of gas on the graduations of the inner tube, which is so arranged that it gives, not the quantity of gas, but the percentage of urea which has been calculated from it. Say that the percentage on the tube is 1·5; this must be corrected for temperature and pressure, and the method of doing this can be found in any general work on physics.

It is important to see that the bung or cork and the tubes fit well and continue in good order; this can easily be tested by raising the inner tube and clamping its openings when it is full of air; it can then be lowered into the water, and if the fluid rises into it, gradually replacing the air, there is a leak, which must be found and repaired.

Uric Acid.—The process originally described by Professor Haycraft in the *British Medical Journal*, 1885, vol. ii., p. 1110.*

Apparatus.—A water or mercury suction pump, to be obtained from Griffin or other instrument-makers.

A flask fitted with a rubber bung perforated in two places. A small funnel is fitted into one of these perforations and an elbow tube into the other.

The elbow tube communicates, by means of a rubber tube, with the suction pump, and the funnel is half filled with broken glass, the surface of which is shaken level, and then a pulp of asbestos, shaken up with water, is poured on to it, and the water allowed to run

* NOTE.—This process will be found given in Hoppe-Seyler's "Handbuch der Chemischen Analyse," p. 359, Berlin, 1893; Hammarsten's "Lehrb. der Physiolog. Chem.," 2nd edition, Wiesbaden, 1891; Neubauer and Vogel's "Analyse des Harns," last edition; Sutton's "Volumetric Analyses"; Sheridan Lea's work, "The Chemical Basis of the Animal Body; and other text-books of physiology.

through while the suction pump is worked, till a uniform felt of asbestos ¼ in. thick has collected on top of the broken glass; this is further washed by passing distilled water through it till the washings are clear of fibre, and then the filter with suction pump attached is ready for use.

The other things required are several glass flasks of 100 to 200 cc. capacity, a 10 cc. and a 50 cc. measure glass, and several pipettes graduated to ½ cc.

The following chemicals are necessary* :—

Bicarbonate of soda.
Strong ammonia, specific gravity ·880.
Ammoniated silver nitrate solution.
Special dilute nitric acid.
Ferric alum, a saturated solution.
Centinormal ammonic thiocyanate solution.
Strong solution of common salt (NaCl).
Bottle of distilled water.

All being ready, a sample of 25 cc. of the twenty-four hours' urine should be measured out and placed in a glass flask.

Before doing this I always note the colour, clearness, specific gravity, and the acidity (as above) from the whole bulk. If there is a turbidity or a deposit of urates, and if, as is generally the case in these circumstances, there is a high specific gravity, *i.e.*, above 1020, I generally add to the whole bulk an equal volume of warm water, which, as a rule, clears it completely.

If in addition there is a deposit of red pepper crystals at the bottom of the collecting glass (and it is well to have a 3,000 cc. glass jar graduated to 50 cc. and fitted with a bung for collecting the twenty-four hours' urine), I generally warm the whole bulk of the urine, adding some bits of solid caustic potash (the acidity having been previously estimated), and shaking till it is clear that all the uric acid has passed into solution.

A 25 cc. sample is then taken, and it must be cooled by placing the flask in cold water before proceeding.

To this add bicarbonate of soda (Haycraft says 15 gr., Herman says 30), about 30 gr. or a little more, then 2 or 3 cc. of the strong ammonia, and about 2 cc. of the ammoniated silver nitrate solution. This last brings down a gelatinous precipitate of urate of silver, and if there is much of it, the fluid is quite thick and rapidly comes to rest after shaking round the flask.

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* These chemicals, with directions for carrying out the process, can be obtained from Messrs. Savory & Moore, 143, New Bond Street, W.

If the patient is taking an iodide it will be necessary to add far more of the silver solution than the 2 cc. mentioned, but I will return to this point again.

We have now a precipitate of urate of silver, together with silver not combined with uric acid, in an alkaline solution; the next process is to separate the silver combined with uric acid from that not combined with it.

The liquid containing the precipitate is now thrown on the filter, and the suction pump put in action; the gelatinous urate of silver remains on the filter, the fluid passes through, and the urate on the filter is washed with distilled water till the fluid passing contains no trace of silver.

The best way to ascertain this is to take two test tubes, and in one of them place 1 to 2 cc. of salt solution, and then pour into both test tubes some of the liquid passing through the filter. So long as the liquid in the tube with salt solution is distinctly more turbid than that in the tube without salt solution, more washing is required.

When the urate precipitate is thus got quite clear of uncombined silver, the special nitric acid solution is poured over it, filling the filter up to the top, and keeping it full for a minute or two by pouring a little more on as it runs down.

As soon as all the nitric acid with the urate of silver in solution has run through, fill the filter up with distilled water and let that also run through, and we are now ready for the final stage of the process.

Take the flask containing the urate of silver dissolved in nitric acid and water, detach it from the suction pump by removing the rubber bung.

Add to the solution two or three drops of the ferric alum solution (indicator) and run in from a graduated pipette the ammonic thiocyanate solution till a permanent pink colour is produced. Read off the amount of thiocyanate used in cc., say it is 18 cc.; then 18 × ·00168 gives the amount of uric acid in 25 cc. of urine, *i.e.*, ·03024 grammes, and this multiplied by 4 gives grammes in 100 cc. = ·12096, and this multiplied by the amount of urine passed gives the total uric acid for the twenty-four hours in grammes.

When the urine contains iodides, the silver combines first with the iodide, and second with the uric acid; in other words, till enough silver has been added to combine with all the iodide present urate of silver is not formed, so that if only the ordinary quantity of the ammoniated silver solution is added the amount of uric acid may be under estimated.

The best way out of this difficulty is to add at once 4 cc. to 6 cc. of the silver solution, then to filter and add to the filtrate more silver solution, and see if any more iodide of silver comes down; if it does filter again, again add more silver; when iodide ceases to form on the addition of the silver solution add 2 cc. of that solution and filter finally; you will now get all the uric acid combined with silver and retained on the filter, and you can then proceed as before.

By this process, which I owe to the kind suggestions of Mr. J. E. Saul, F.I.C., I have been able to obtain the same amount of uric acid from a urine both before and after addition of an iodide.

Haycraft's process takes from thirty to forty minutes to complete; longer for high specific gravity urines, shorter for dilute, for much urate of silver clogs the filter and increases the time required for the washing process; so that time is saved by diluting high specific gravity urines; but when a urine of specific gravity 1025 is diluted to 1 in 4 there is probably some increased loss of urate in the washing process, as urate of silver is not absolutely insoluble in water; on the other hand, the gelatinous urate clogs the filter and aids its own separation, which, up to a certain point, is more perfect the more there is of it.

Haycraft's process thus described, while taking quite a moderate amount of time, gives very accurate and constant results; where there is any doubt I repeat my observation, and rarely find a difference of more than $\frac{1}{2}$ cc. of thiocyanate solution between the two; if there is a greater difference than this I go in for further investigation, and may find that a fragment of glass has perforated the asbestos and put the filter wrong, and when this has been put right I again repeat my observation.

Though the process takes thirty to forty minutes to complete, a large part of that time it requires only an occasional look to add water when it runs through, and other matters can be attended to, and then, if the suction pump is powerful, several filters can be connected with it and several urines worked through at the same time.

It is a distinct advantage of this process that it can be worked on 25 cc., or even $12\frac{1}{2}$ cc., of a high specific gravity urine, for when the urine of a single hour or less, which you may want to estimate in a case of headache, fits, or paroxysmal hæmoglobinuria, amounts only to 20 cc. or 30 cc., processes which require 50 cc. or 100 cc. of urine cannot be used; and it would by other processes often be quite impossible to estimate the uric acid in small quantities of blood, muscle, or other organs which can be done by this process.

Haycraft's process has been criticised by various writers and others who have invented processes of their own and who have no doubt reasons that seem to themselves to be quite satisfactory for believing these processes to be more accurate than any other. But watching the matter as I have for many years I have become more and more convinced of the great accuracy of this process, and think there is really little to be said in favour of other processes which have often been considered by writers on the matter to be more accurate. As a single instance of this I will take an article by Dr. Walker Hall, *British Medical Journal*, 1906, vol. i., p. 128, in which he shows that the so-called "accepted processes," those of Salkowski and Hopkins, show differences amounting to from – 33 to + 96. He points out that it is absurd to judge any other process by methods that differ so much. He is here expressing what I have always felt: that we have not yet arrived at that stage of perfection in the estimation of uric acid by chemical processes which justifies us in setting up any one process as the standard; but I will assert that whenever this comes to be done Haycraft's process has quite as good a claim as any other known to me. But those who will insist on taking one of the other processes above named as the only standard and looking on all other results as erroneous, have only themselves to thank if they find that this leads them into error.

To estimate the uric acid in organs and tissues I have used a process given by Salkowski and Luebe ("Die Lehre von Harn," p. 94) for blood.

It consists simply of throwing the blood or tissue finely divided (I pass solid tissues through a mincing machine) bit by bit into ten times its volume of boiling water. The coagulated albumin is removed by filtration or decantation, and the fluid evaporated down to about the bulk of the original blood or tissue. I then apply Haycraft's process just as for urine (see remarks on p. 7).

As I found that long boiling of tissues appeared to increase the amount of uric acid obtained from them, I adopted the uniform plan of boiling for half an hour after all the tissue is in the water.

It is by this process that I obtained the results given in chapters ii. and xvii. When tissues contain uric acid visible under the microscope or to the naked eye, this process yields a very large quantity, and the final evaporation need not be carried so far.

Supposing, however, that such great accuracy is not required, and that for clinical purposes all one wants to know is that a patient is passing about half as much uric acid again to-day as he was yesterday, or that the urine which was excreted at the time of a

fit or headache or an attack of paroxysmal hæmoglobinuria contains two or three times as much as that passed in the previous hour when these troubles were absent; this knowledge can be arrived at in a very few minutes and without much trouble.

I have been pointing out now for years that the urinary water is both from hour to hour and from day to day inversely as the uric acid excreted along with it, so that by measuring the water from hour to hour we can estimate the greater or less amount of uric acid excreted along with it.

If the water in any hour is twice as much as in the previous hour, the uric acid will probably be only one-half of what it was, or *vice versâ*, provided there is some water in the body to be excreted, and provided there has been no hæmorrhage, vomiting, or diarrhœa to remove all the available water from the body.

Taken over a long period of time, my lowest excretion of water is about 700 cc. to 800 cc. in twenty-four hours, or about 30 cc. an hour, and with this the excretion of uric acid in relation to urea varies from about 1—18 up to 1—25.

On the other hand, my largest excretion of water is about 2,000 cc., or about 80 cc. an hour, and this corresponds to a relative excretion of uric acid of about 1—35 to 1—45.

In single hours the excretion may fall below 30 cc., or rise a good deal above 80 cc., but the urine is most scanty in those hours of the day in which the excretion of uric acid is greatest, and most profuse in those in which it is least (see fig. 3).

If when the urine is scanty there is a doubt whether this is due to collæmia and retention of water (*i.e.*, if there are no other signs of collæmia being present), the blood should be examined, and if the scanty urine is due to collæmia and retention of water it will be found to be dilute (*i.e.*, both hæmoglobin and red cells will be relatively diminished), but if the scanty urine is due to want of water in the body, it having been removed by the skin or bowels, &c., then the blood will be concentrated (*i.e.*, both hæmoglobin and red cells will be relatively increased). In this latter case no inference can be drawn from the urinary water as to the presence or absence of collæmia.

But bearing these things in mind, if at any time, as often occurs in the uric acid headache, epilepsy, or hysteria (see case records in chapter vii.), the urine is 30 to 40 cc. in one hour, and 100 cc. or above in the next, no fluid having meanwhile been swallowed, if the urea is estimated in both hours one will not be very far out if one puts uric acid as 1—20 of urea in the first hour, and as 1—40 in the

second, and precisely the same if the water fluctuation occurs in days instead of hours.

For many clinical purposes, and when the uric acid excretion is not required in grains for publication, this is all that one wants to know, and I am in the habit of thus reasoning from the water to the uric acid in scores of cases which I should have no time to estimate, making an estimation here and there to support my inference if there seems to be any reason to doubt it.

Again, as pointed out with reference to fig. 5, the difference between the temperature in the mouth and that in the rectum will often give a very decided indication of the quantity of uric acid in the blood, and when this agrees with the record of the urinary water there is not much room to doubt.

Lastly, the quantity of uric acid or xanthin present can be demonstrated in the blood itself (see p. 92), and the capillary reflux and the blood pressure will also tell of the quantity present, and so accurate are these records that quite small quantities swallowed intentionally can be seen as they pass through the blood (see fig. 75), so that in most clinical cases it is a needless waste of time and energy and a useless trouble to the patient to collect the urine at all.

Blood Decimal.—I have estimated the cells and hæmoglobin with the hæmocytometer and hæmoglobinometer of Sir W. Gowers, and the decimal spoken of by Dr. A. E. Garrod and others as "worth" is obtained by dividing the percentage of hæmoglobin by the percentage of red cells, thus $\frac{\text{per cent. Hæmoglobin}}{\text{per cent. Red Cells}}$; if both are at the supposed normal (100), the result is a whole number, and not a decimal; but a decimal is generally obtained which represents the hæmoglobin value of each red cell. This is as low as ·3 or less in chlorosis, and ·6 to ·7 or above in more normal conditions.

As mentioned in chapter xii., it is necessary for reasons there given to add ·3 to the figures on the card and 1·5 to those in the book to make them comparable to the results with other instruments. Thus on the card ·8 should be 1·1 and ·2 should be ·5, and in the book ·7 should be ·85 and so on.

A hæmoglobinometer and hæmocytometer have been brought out by Dr. Oliver, the inventor of the arteriometer, to be presently mentioned. The hæmoglobinometer is an adaptation of an instrument used commercially for determining shades of colour. It has to be used by the light of candles of constant power.

The hæmocytometer depends on an observation by Dr. Oliver that the appearance of the reflection of the candle as a streak of

light through a mixture of blood and diluting fluid in a special tube always corresponds with the presence of a definite number of cells; hence the tubes can be graduated in per cents. to correspond with the dilution required to bring out the streak of light.

I have used both these instruments, and compared them with those of Sir W. Gowers, and I find Dr. Oliver's hæmoglobinometer very useful in the dark days of winter, when one has to work by artificial light, but on the whole I prefer Sir W. Gowers' instrument when daylight is available. Dr. Oliver's hæmocytometer is easy to work with when you have got into the way of using it; the results are fairly quickly obtained, and with care appear to me to come very close indeed to those obtained by counting.

Water in Expired Air.—I have estimated this by means of U tubes filled with calcium chloride; each arm of the tube is about 8 in. long, and has a diameter of little less than 1 in. It is closed at each end by a rubber bung perforated by a glass tube bearing a bit of rubber tubing and a glass mouth-piece on one end; the rubber tubes are closed by spring clamps. The whole is carefully weighed before use and again afterwards, and the difference recorded equals the moisture in the expired air. It is used as follows:—

Remove the clamp from the rubber tube at the far end of the U tube, and place the glass mouth-piece on the near end between the lips. Sitting quietly and comfortably, and when respiration is quite regular, and the second hand of a watch is at a given place, begin to expire through the tube between the lips, inspiring through the nose; the clamp on the near tube is to be opened at each expiration and closed at its end. After a little practise it is possible to continue to respire quite regularly, and to open and shut the tube at the right moment in each act. This is continued for five minutes by the second hand of a watch on the table; the clamp is then shut and the distal tube also clamped, and the U tube is ready to be weighed.

Messrs. Savory and Moore kindly did the weighing for me, as I have no instruments sufficiently accurate.

I measured the urine passed in fifteen minutes, including the five minutes of expiratory estimation, and divided the result by three to compare with the expired water in five minutes.

The results show that when the urinary water is scanty owing to collæmia, the expired water is also scanty, and this affords the best proof that uric acid affects the capillaries in the lungs as well as those in the kidneys and elsewhere throughout the body.

Pulse Tension or Blood Pressure.—Apart from the signs to be obtained by an educated finger on the radial artery and an educated ear at the apex and base of the heart, the sphygmograph furnishes a good clinical record of arterial tension, and has this further advantage, that the tracing can be kept indefinitely for comparison with all future tracings.

There is no doubt that the sphygmograph is but an indifferent gauge of blood pressure, but it tells us what is clinically of far more value—the effect which obstruction of capillaries produces on the heart and large vessels behind them; that, in two cases lying side by side, the actual blood pressure may be identical, but in one case, say, with a well-nourished and hypertrophied left ventricle, this blood pressure may be produced by a slight obstruction of capillaries, while it produces almost no effect except a little slowing of the heart's action; in the other case, with an ill-nourished heart, the pressure may be produced by considerable obstruction of capillaries, while the heart is acting irregularly, palpitating and fluttering, in a word, failing and dilating before the peripheral resistance; all this the sphygmograph will tell us with considerable accuracy, while to be told that the blood pressure is the same in these two cases is information of almost no clinical value.

I have used the sphygmograph of Dudgeon, and have had one fitted with a pen, the invention of my friend, Mr. W. H. Symons, which I believe to be a great improvement on the old point scratching on smoked paper.

The pen consists of a little cone of metal, open at both ends, and threaded with a bit of cotton. The small end of the cone with the cotton below it rests on the paper, and is moved over it in exactly the same way that the old point was moved.

The only thing to attend to is that the paper must be highly glazed and very smooth, to reduce friction, and then the pen runs over it perfectly, making curves which are identical with those obtained by the old process. The instrument thus modified, with directions for use, can be obtained from Messrs. Maw, Son and Sons, London.

The pen works best with a solution of aniline, a little of which is placed on the upper end of the cone and is conducted down by the cotton.

In this way there is no limit to the number of tracings that can be taken, as paper after paper can be passed through the machine, so as to catch irregularities of the pulse, which only occur now and again, or a continuous tracing can be made on paper several feet

long. The tracing is permanent from the moment it is made, and there is no black to rub off and no fixing required, so that this useful invention renders the process both more cleanly and more expeditious, and is a great help to clinical recording. I have already mentioned Dr. Oliver's inventions—the arteriometer and the pulse pressure gauge—to be obtained from Hawksley, of Oxford Street, and have said that I believe they may be found to be of very great clinical value for recording changes of blood pressure produced by uric acid, or by drugs which act upon it, and have given some instances in which this appeared to be so. My results, so far as they go, are very favourable to their accuracy and the value of their records; and it will be seen that I have used the arteriometer in several figures and elsewhere to obtain indications of blood pressure.

One is no doubt liable to make errors with the arteriometer by not getting exactly over the artery, which one may manage fairly well on one occasion and not on the next; but this error is always on the side of making the diameter of the artery appear too great, so that the smallest reading to be obtained is the most correct, and the best way is to make repeated observations with the object of obtaining this. My results with this instrument generally agree among themselves, like conditions yielding like results, and also with the changes in the rate of the heart's action and of the sounds at the apex and base. Of the three I regard the changes in the rate of action as the best guide in physiology, so constant and true is Marey's law; but when all three agree there is not much room for doubt that the diameter of the artery has been correctly measured.

The sphygmometer mentioned in reference to figs. 38 to 43 and 75 is to be obtained from Messrs. J. and J. Hicks, of 10, Hatton Garden, E.C. The small form, price 30s., can easily be carried in the pocket.

I gather from an interesting article by Dr. C. J. Martin, in the *British Medical Journal*, 1905, vol. i., p. 865, that an instrument which has only a small surface of rubber applied to the artery is liable to give results which are too high, and from what I have been able to learn elsewhere an error of 10 to 15 per cent. may be thus introduced. One can easily understand that this may be so, for unless the surface of rubber is rather large it is obvious that the artery in expanding will have to overcome some force besides the pressure within the tube, of which the rubber forms one boundary.

But what we want in clinical medicine is the relative result, and

if all our figures are 15 per cent. too high they are still accurate and reliable for comparative purposes. The amount of error can be gauged by comparison with another instrument if necessary, or those who have normal blood pressure can use this as a means of gauging the amount of error in their instrument. Personally I have always found this little instrument give results which corresponded in every way with the other conditions present, results which, as I have previously pointed out, proved to have a practically constant relation to the rate of the capillary reflux, and it is hardly possible for an instrument which gives such constant results to be altogether unreliable. I should say that I have always exercised great care to apply the instrument to a part of the radial artery where it was as free as possible from overhanging bone or tendon. I can, however, well understand that people who do not take this precaution, and who have not had a long experience of the instrument and the errors that may thus be introduced, may occasionally get somewhat extraordinary results. Taking the capillary reflux as a guide, one can practically obtain the point of maximum oscillation on this instrument by multiplying the reflux by 20. Thus we get :—

Fever C.R. 3—4 × 20 = B.P. (point of max. oscillation) 60—80 mm. of Hg.
Normal C.R. 5—6 × 20 = B.P. 100—120 mm. of Hg.
Raised C.R. 7 × 20 = B.P. 140.
,, C.R. 8 × 20 = B.P. 160.
,, C.R. 9 × 20 = B.P. 180.

When the pulse is too quick the B.P. may be a little below the above ratio, *i.e.*, C.R. 7, P. 90, B.P. 130. If the pulse is too slow it may be the other way, *i.e.*, C.R. 7, P. 60, B.P. 150. In the former case part of the slowing of the C.R. is due to cardiac weakness ; in the latter it is all due to capillary obstruction, and the heart is strong and acting slowly.

The capillary dynamometer also used for these figures is to be obtained from T. Hawksley, 357, Oxford Street, W., price 10s. 6d. It can be carried in the waistcoat pocket, and my results with it have been obtained with 15 oz. pressure applied for six half seconds.

With these two instruments we can tell all variations of the capillary circulation and the blood pressure, and a great deal as to the cause of the variations.

Thus a slow capillary reflux (*i.e.*, more than six half seconds) with normal or low blood pressure, means a weak heart, for the capillaries are obstructed, but the pressure is not raised because the heart is weak. This condition is met with in some forms of morbus

cordis, especially where there is dyspnœa with heart weakness, in the heart failure of Bright's disease or pneumonia, and in post-febrile conditions after long fevers, such as enteric, when the heart has been weakened by the fever.

As a rule, a quick capillary reflux is found with a pressure below 100 and means fever.

And a slow reflux with a more or less raised pressure, in accordance with the strength of the heart, is found in all conditions of collæmia, *e.g.*, dyspepsia, colic, Bright's disease, diabetes, obesity, post-febrile conditions, &c.

Thus the capillary reflux is the guide to the amount of uric acid in the blood, and, with the blood pressure, tells us also the strength or weakness of the heart.

As we see the capillary reflux × 20 gives the corresponding blood pressure, *e.g.*, a capillary reflux of six half seconds will show a blood pressure of 120, or one of seven a blood pressure of 140. But if the heart is weak and the *vis a tergo* deficient, the blood pressure will be lower, *e.g.*, 100 for a capillary reflux of 6 or 140 for a capillary reflux of 8 half seconds, and then also (as a further sign of heart weakness) the pulse will be above the normal rate though temperature is subnormal.

In myself a capillary reflux of six half seconds or above corresponds with a uric acid excretion of ·6 gr. an hour and above; while one of four to five half seconds corresponds with an excretion of ·3 to ·4 gr. per hour, and with very slight variations this holds also for others; and in Bright's disease, with a reflux of twelve half seconds, we get an excretion of ·75 gr. per hour or more, and in fever, with a reflux of two or three half seconds, we get an excretion of ·25 gr. per hour or less, and the blood granules correspond with and can be used to confirm these results.

The reflux can also be slowed or quickened at pleasure by drugs that affect the quantity of uric acid in the blood, and it is mechanically quickened by local or general venous obstruction, as Raynaud himself pointed out.

The mean blood pressure is the point at which the column of fluid in the sphygmometer makes the largest excursion up and down, when it is pressed over the artery.

It is necessary to get the instrument fairly over the artery, to get a good movement of the column of fluid and to observe it in a good light.

The capillary dynamometer has the advantage of giving a constant area of pressure and a known and measurable pressure,

and time can be measured by the second hand of a watch or by counting half seconds, which it is easy to learn to do, or when at home by a metronome beating half seconds.

Though such marked differences as Bright's disease on the one hand and fever on the other can be distinguished at once with the point of the finger, it is better to use the more accurate capillary dynamometer and some measure of time when small differences have to be estimated, as between the amount of uric acid in the blood of morning and evening, or the slight fluctuation of a little exposure to cold, a dyspepsia, or a little mental depression; but with these instruments the real fluctuations in the excretion of uric acid from day to day can be distinguished with very considerable accuracy, as seen in figs. 38 to 43 and 75.

In very many, if not most, cases it is now quite useless to trouble the patient to collect the urine, for the uric acid in the blood can be directly estimated in a few minutes from the capillary reflux or the blood granules; and as regards hour to hour and day to day fluctuations this is quite sufficient; while for longer periods the blood decimal is an absolutely certain index of the quantity of uric acid that is passing through the blood over days and weeks; and the fact that a patient has not been quite faithful to diet during a holiday is often evidenced by a fall in the blood decimal which is visible on his return to town.

APPENDIX I.

Notes on Diet.

We generally depend for our nitrogen upon substances containing albumens, and it is the habit of this country at the present day to get it almost entirely from flesh albumens, in ignorant disregard of the poison that animal tissues contain.

It can be calculated from the data given in works on physiology that a man, in order to get enough nitrogen, must be supplied with from 9 gr. to 10·5 gr. of albumen per day for each pound of body weight. Children require more; thus a child of 35 lb. weight may require as much as an adult three times his weight, and this gradually diminishes until the adult standard is reached, while old and very sedentary people may require considerably less than the adult allowance.

But given a sufficient quantity of albumen, nutrition, strength and power of endurance should be not only as good on vegetable and milk albumens as on those of flesh origin, but better, as much friction in the machinery is saved by excluding uric acid. The vegetable albumens are, in my experience, completely digested and absorbed; so that the nitrogen, calculated from their percentage composition, is generally identical with the nitrogen obtained from the excretions.

The animal foods in common use (meat, fish, fowl, game, eggs)* all contain uric acid, or substances of the xanthin group which can be converted into it. The alkaloids of tea, coffee, chocolate, and cocoa are also xanthins; and certain other vegetable substances, as the pulses (peas, beans, lentils, pea-nuts, &c.), cashew nuts, asparagus and mushrooms, contain large quantities of xanthin, and are to be avoided; while wholemeal and brown breads and oatmeal are open to a similar objection as there is some xanthin in the outer husk of most grains.

The prevention or cure of diet diseases requires that the body and blood be cleared of all excess of uric acid, but it is obviously impossible to do this while these substances are continually introduced with every meal that is eaten. And in contradiction of old theories we now *know* by experience that all uric acid diseases can be prevented or cured by refusing to swallow it.† Those who swallow 8 gr. to 12 gr. per day (equal to nearly 8 oz. to 12 oz. in a year) are

* These animal flesh foods may be said to contain from 15 to 25 per cent. of albumens.

† In fact, they are not diseases but poisonings by unnatural food.

and remain, diseased; those who cease to swallow it in the above-named poisonous foods *gradually draw free*, in eighteen months to two years, from uric acid and its effects. It is also necessary not to eat much more than the above physiological allowance of albumens, for if this is exceeded uric acid will be formed in some slight excess, and part of this excess may be retained in the body. There is, however, one animal food, namely, milk and its products, as cheese, that contains little or no uric acid or xanthin, and the chief foods available for a *uric-acid-free diet* are as follows:—

Breadstuffs, as bread, macaroni, rice and other cereals, biscuits and puddings. And these, with a small quantity of milk and cheese, and some nuts or almonds, form an amply sufficient diet for anyone.*

Then potatoes, vegetables and fruit are to be regarded as sauces or additions.

As whole nations are often practically dependent on a single one of these substances, those who cannot live on a mixture of them all must be hard indeed to feed.

And now, applying the rule of the relation of albumens to body-weight: A young adult weighing (after deducting weight of clothing) 10 st., or 140 lb., and leading a hard-working life, must consume 140×10† $= 1{,}400$ gr. of albumen per day, and these might be got as follows:—

‡19 oz. breadstuffs‖ (8 per cent. albumens	= 34 gr. per oz.)	= 646 gr.
2 pints milk (3 per cent. albumens	= 13 ,, ,,)	= 525 ,,
1 oz. cheese§ (33 per cent. albumens	= 140 ,, ,,)	= 140 ,,
11 oz. vegetables and fruit¶ (2 per cent. albumens	= 8 ,, ,,)	= 89 ,,
		1,400 ,,

* About 3 oz. of bread, or 7 oz. to 8 oz. of milk, are equal to 1 oz. of meat, and 1 oz. of cheese is equal to 1½ oz. meat, while almonds are equal to their own weight of meat, and another method of changing diet is to replace the flesh foods by their equivalents.

† For middle-aged or sedentary people it will be sufficient to multiply by 9, and those who are stout should take their body-weight before they became stout, while for old people 8 will often be enough.

‡ These are the ordinary foods which everyone takes, flesh being left out and the others increased to prevent diminution of albumen. Avoid all foods of unknown composition. Beginners should report every three months at first.

‖ A great part of this may be taken as rice or macaroni, and 1 oz. of nuts is roughly equal to 2 oz. of breadstuffs; or part of the breadstuffs may be replaced by increasing the cheese.

§ 1 oz. of cheese is roughly equal to or may be replaced by half a pint of milk; 4 oz. of bread are equal to 1 oz. of cheese or half a pint of milk. For further information see "Diet and Food," Churchill, London. 6th Ed., 1906. Price 2s.

¶ From October to April this should be chiefly vegetable, of which potato is the best. In summer, fruit which is in season may be taken equally with vegetables.

If this man lives and works in the open air, he may have such a good appetite for bread, macaroni, rice, potatoes, nuts* and fruit that no milk and cheese will be required; but those who live in towns and are more sedentary will generally require to add these latter to a greater or lesser extent. This rule, regulating quantity of albumen by body weight, must never be broken.

No attempt must be made to live on vegetables and fruit alone. Cereals, milk, cheese, and nuts are the nourishing foods, and vegetables and fruits are palatable additions if liked. Fruits should be taken chiefly when in season, *i.e.*, in summer, and very little in winter. It is, however, possible to live on milk and cheese with potatoes and fruit and no bread at all; and in the potato and fruit season this is a pleasant and palatable diet, but then milk and cheese must be increased to make up for the absence of bread and cereals, allowance being made for the increase of potatoes and fruit (see Appendix II.).

It is also possible to live on breadstuffs, with nuts, almonds, and the more nourishing dried fruits, without any milk or cheese at all, and this diet can be used to diminish obesity. Some can live on nuts, almonds and fruit alone, and this is perhaps the best diet of all for the young and strong, though it is rarely possible for those who are diseased or dyspeptic, especially if the teeth are bad.

Many of these diets have the advantage that while introducing little or no xanthin or uric acid, they keep the blood supplied with the alkaline salts which it requires, and thus aid the solution and removal of uric acid introduced into the body by previous wrong diets. This removal, however, will produce some *temporary* effects, such as depression and anæmia, which beginners must remember to credit to their true source, viz., the passing through the blood of the poisons from the old flesh and tea diet.

Taking the above figures as approximately correct, a diet scale can be calculated for any individual whose weight is known which will enable him to find his feet on the new diet, and meet his wants for himself, as he did on the old one.

* Nuts should only be taken by those whose teeth and digestion are sound, and who have been in the habit of taking them on ordinary diet.

APPENDIX II.

Scheme for Alteration of Diet.

1st Stage.—Give up tea, coffee and meat soups. Replace by milk, milk and water, soups made with milk, &c.*

2nd Stage.—Alter Breakfast.—Leave out bacon, egg, or fish. Replace by an increase of toast, biscuits and breadstuffs, and half to three-quarters of a pint of milk.†

3rd Stage.—Alter Lunch.—Leave out fish, meat, fowl or game. Replace by an increase of toast, biscuits, breadstuffs and puddings, half a pint of milk and 1 oz. of cheese.

4th Stage.—Alter Dinner.—Leave out fish, meat, fowl or game. Replace by an increase of toast, biscuits, breadstuffs and puddings, a cheese dish and half a pint of milk.‡

Follow this scheme out stage by stage, making each stage complete and satisfactory before the next stage is begun, and it is well to take several weeks over the stages as sudden alterations of diet are, as a rule, to be avoided.

It is necessary to learn to take the new foods, and where this can only be done gradually, the old foods must not be entirely given up till it has been learnt, and can be practised with comfort.

Those who have difficulty in digesting breadstuffs should take them as dry as possible (toasted bread, biscuits, &c.), except for a little butter, and drink the milk or other fluid towards the end of the meal. They should also keep breadstuffs apart from fruit in any form, take fruit only when in season and in a meal by itself (*e.g.*, the 5 o'clock meal).

Beer, wines and spirits may be continued by those who are in the habit of taking them with meals, provided they are found to help digestion. They should, however, be completely avoided after the

* In summer and in hot countries many nice drinks can be made, like barley water, and flavoured with lemon or apple peel or other fruit.

† Those who cannot digest any breadstuffs may yet be able to take vegetables freely and fruit also when in season, and a diet composed of several pounds of these with the addition of two pints of milk and 3 oz. of curd cheese (equivalent to 2 oz. of ordinary compressed cheese) eaten with them, will furnish about 1,300 gr. of albumen. Each meal would then consist of vegetables or fruit or both, with milk or cheese or both. After living on this diet for some time they may be able to add some breadstuffs, especially rice and twice-baked bread. Curd cheese is made by adding fruit juice to fresh milk (*e.g.*, juice of two lemons to one quart of milk) and straining off the whey under pressure in a cheese cloth.

‡ Absolute quantities depend on body weight (see Appendix I).

diet changes have been in operation for some time and have proved satisfactory, for stimulation, like drug taking, is always wrong, except as a temporary measure.

The same applies to fruit, which, especially in a cold climate, must be taken only when in season (grown out of doors, not forced). Exposure to cold or the taking of fruit out of season produces stimulation at the time, but all stimulation is wrong. It means retention of uric acid and must lead later on to more or less recurrence of the old troubles. The diet for a cold climate is one of breadstuffs, milk, cheese and vegetables; clothe warmly and live in warm houses. Be strong because you are well nourished and uric-acid-free, not because you are braced by cold or stimulated by fruit or wine or drugs.

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